STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 156426

TO: Ben Sackey **Location: 5c31/5c18** **Art Unit: 1626** **Thursday, June 16, 2005** **Case Serial Number: 10/625558**	**From: Noble Jarrell** **Location: Biotech-Chem Library** **Rem 1B71** **Phone: 272-2556** **Noble.jarrell@uspto.gov**

Search Notes

Access DB# 156428

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: BEN SACKEY Examiner #: 73489 Date: 6/13/05
Art Unit: 1626 Phone Number ~~302~~ -0704 Serial Number: 10/625,558
Mail Box and Bldg/Room Location: REM 5B31 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Process for the preparation of Naproxene nitroxyalkyl esters

Inventors (please provide full names): Benedini et al.

Earliest Priority Filing Date: 7/27/00.

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

4-nitroxybutyl ester of 2-(S)-(6-methoxy-2-naphthyl) propionic acid

****

STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: NOBLE	NA Sequence (#)		STN	✓
Searcher Phone #:	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)	1	Questel/Orbit	
Date Searcher Picked Up:	Bibliographic	✓	Dr.Link	
Date Completed: 6/16/05	Litigation		Lexis/Nexis	
Searcher Prep & Review Time: 5	Fulltext		Sequence Systems	
Clerical Prep Time:	Patent Family		WWW/Internet	
Online Time: 15	Other		Other (specify)	

PTO-1590 (8-01)

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=> b reg
FILE 'REGISTRY' ENTERED AT 09:55:46 ON 16 JUN 2005
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES:   15 JUN 2005  HIGHEST RN 852355-71-6
DICTIONARY FILE UPDATES:  15 JUN 2005  HIGHEST RN 852355-71-6

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TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

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*************************************************************************
*                                                                       *
* The CA roles and document type information have been removed from     *
* the IDE default display format and the ED field has been added,       *
* effective March 20, 2005.  A new display format, IDERL, is now        *
* available and contains the CA role and document type information.     *
*                                                                       *
*************************************************************************

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide l5 tot

L5   ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   170591-17-0  REGISTRY
ED   Entered STN:  23 Nov 1995
CN   2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl
     ester (9CI)  (CA INDEX NAME)
FS   3D CONCORD
MF   C18 H21 N O6
SR   CA
LC   STN Files:   CA, CAPLUS, CASREACT, PROUSDDR, SYNTHLINE, TOXCENTER,
       USPATFULL
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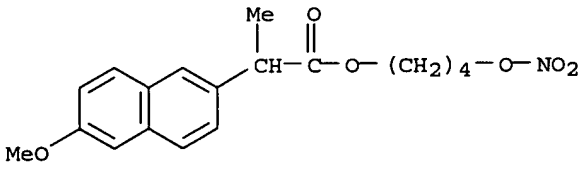


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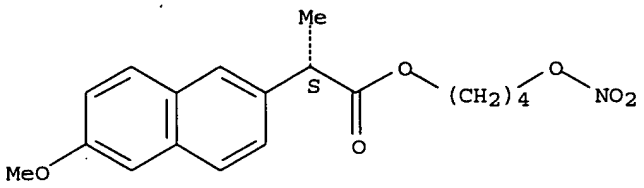
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

               9 REFERENCES IN FILE CA (1907 TO DATE)
               9 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5   ANSWER 2 OF 2  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   163133-43-5  REGISTRY
ED   Entered STN:  19 May 1995
```

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (S)-
OTHER NAMES:
CN (S)-2-(6-Methoxy-2-naphthyl)propanoic acid 4-nitrooxybutyl ester
CN AZD 3582
CN HCT 3012
CN Nitronaproxen
FS STEREOSEARCH
MF **C18 H21 N O6**
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, CA, CAPLUS, CASREACT, CIN, EMBASE, IMSDRUGNEWS, IMSRESEARCH, PHAR, PROMT, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

25 REFERENCES IN FILE CA (1907 TO DATE)
26 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d his full

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FILE 'REGISTRY' ENTERED AT 09:53:24 ON 16 JUN 2005
L1 656 SEA ABB=ON PLU=ON C18H21NO6
L2 QUE ABB=ON PLU=ON (PMS OR MAN OR IDS)/CI OR UNSPECIFIED OR COMPD OR COMPOUND OR (D OR T)/ELS
L3 642 SEA ABB=ON PLU=ON L1 NOT L2
L4 16 SEA ABB=ON PLU=ON L3 AND C6-C6/ES AND NR=2
D STR TOT
SEL RN L4 7-8
L5 2 SEA ABB=ON PLU=ON (163133-43-5/BI OR 170591-17-0/BI) AND L4
D IDE L5 TOT

FILE 'HCAPLUS' ENTERED AT 09:55:59 ON 16 JUN 2005
L6 40 SEA ABB=ON PLU=ON L5 OR 2 (1A)(NAPHTHALENEACET? OR NAPHTH?(1A)ACET?)(1A)6(1A)METHOX? (1A)METHYL(1A)((NITROOXY OR NITROXY)(1A)BUTYL OR NITROXYBUT? OR NITROOXYBUT?) (1A)ESTER? OR AZD3582 OR HCT3012 OR NITRONAPROXEN#
L7 8 SEA ABB=ON PLU=ON METHOX?(1A)NAPHTH? (1A)PROPAN?(1A)ACID?(1A)((NITROOXY OR NITROXY)(1A)BUTYL OR NITROXYBUT? OR NITROOXYBUT?) (1A)ESTER? OR AZD(1A)3582 OR HCT (1A)3012
L8 41 SEA ABB=ON PLU=ON (L6 OR L7)
E BENEDINI F/AU
L9 37 SEA ABB=ON PLU=ON ("BENEDINI F"/AU OR "BENEDINI FRANCESCA"/AU)
E OLDANI E/AU
L10 8 SEA ABB=ON PLU=ON ("OLDANI E"/AU OR "OLDANI ERMINIO"/AU)
E CASTALDI G/AU
L11 90 SEA ABB=ON PLU=ON ("CASTALDI G"/AU OR "CASTALDI GRAZIANO"/AU OR "CASTALDI GRAZIONO"/AU)

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L12          71 SEA ABB=ON  PLU=ON  NICOX/CS,PA
L13           1 SEA ABB=ON  PLU=ON  (NI?(1A)COX)/CS,PA
                D BIB
                D BIB L12
L14           8 SEA ABB=ON  PLU=ON  L8 AND (L9 OR L10 OR L11 OR L12 OR L13)
L15          33 SEA ABB=ON  PLU=ON  L8 NOT L14
L16             QUE ABB=ON  PLU=ON  PY<=2000 OR AY<=2000 OR PRY<=2000 OR
                PD<20000727 OR PRD<20000727 OR AD<20000727
L17          13 SEA ABB=ON  PLU=ON  L15 AND L16

     FILE 'HCAOLD' ENTERED AT 10:05:14 ON 16 JUN 2005
L18           0 SEA ABB=ON  PLU=ON  (L6 OR L7)

     FILE 'REGISTRY' ENTERED AT 10:05:34 ON 16 JUN 2005
                SAV TEM L5 SAC558F0/A

=> b hcap
FILE 'HCAPLUS' ENTERED AT 10:06:09 ON 16 JUN 2005
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26, 1996), unless otherwise indicated in the original publications.
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FILE COVERS 1907 - 16 Jun 2005  VOL 142 ISS 25
FILE LAST UPDATED: 15 Jun 2005  (20050615/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d all hitstr l14 tot

L14  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2005:300267  HCAPLUS
DN   142:349032
ED   Entered STN:  07 Apr 2005
TI   Nitrosylated analgesic and/or antiinflammatory drugs having antiviral
     activity
IN   Bolla, Manlio; Santus, Giancarlo; De Soldato, Piero
PA   Nicox S.A., Fr.
SO   PCT Int. Appl., 41 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  A61K031-60
     ICS  A61K031-44; A61K031-216; A61K031-235; A61K031-245; A61P031-12
CC   1-5 (Pharmacology)
FAN.CNT 1
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
PI   WO 2005030224         A1    20050407    WO 2004-EP51551         20040720
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
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NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG

PRAI EP 2003-292378 A 20030926

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2005030224	ICM	A61K031-60
	ICS	A61K031-44; A61K031-216; A61K031-235; A61K031-245; A61P031-12
WO 2005030224	ECLA	A61K031/216; A61K031/235; A61K031/245; A61K031/44; A61K031/60

AB The invention discloses the use of nitrosylated analgesic and/or antiinflammatory drugs for the prevention and/or treatment of viral diseases and/or their complications.

ST nitrosylated analgesic antiinflammatory drug viral disease; antiviral nitrosylated analgesic antiinflammatory drug

IT Analgesics
Antipyretics
Antiviral agents
Common cold
Influenza
Influenza A virus
Influenza virus
Prophylaxis
(nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity)

IT Anti-inflammatory agents
(nonsteroidal; nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity)

IT Drug delivery systems
(oral; nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity)

IT Drug delivery systems
(parenterals; nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity)

IT Drug delivery systems
(topical; nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity)

IT Cardiovascular agents
Cardiovascular system, disease
(viral infection affecting cardiovascular system; nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity)

IT Infection
(viral; nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity)

IT 50-78-2D, Aspirin, nitrosylated derivs. 53-86-1D, Indomethacin, nitrosylated derivs. 61-68-7D, Mefenamic acid, nitrosylated derivs. 69-72-7D, Salicylic acid, nitrosylated derivs. 89-57-6D, Mesalamine, nitrosylated derivs. 103-90-2D, Paracetamol, nitrosylated derivs. 487-48-9D, Salacetamide, nitrosylated derivs. 530-75-6D, Acetylsalicylsalicylic acid, nitrosylated derivs. 530-78-9D, Flufenamic acid, nitrosylated derivs. 644-62-2D, Meclofenamic acid, nitrosylated derivs. 4394-00-7D, Niflumic acid, nitrosylated derivs. 5104-49-4D, Flurbiprofen, nitrosylated derivs. 13710-19-5D, Tolfenamic acid, nitrosylated derivs. 15307-86-5D, Diclofenac, nitrosylated derivs. 15687-27-1D, Ibuprofen, nitrosylated derivs. 19834-23-2D, nitrosylated derivs. 22071-15-4D, Ketoprofen, nitrosylated derivs. 22204-53-1D, Naproxen, nitrosylated derivs. 23049-93-6D, Enfenamic acid, nitrosylated derivs. 26171-23-3D, Tolmetin, nitrosylated derivs. 29679-58-1D, Fenoprofen, nitrosylated derivs. 31842-01-0D, Indoprofen, nitrosylated derivs. 33005-95-7D, Tiaprofenic acid, nitrosylated derivs.

36322-90-4D, Piroxicam, nitrosylated derivs. 36330-85-5D, Fenbufen, nitrosylated derivs. 38194-50-2D, Sulindac, nitrosylated derivs. 38677-85-9D, Flunixin, nitrosylated derivs. 40828-46-4D, Suprofen, nitrosylated derivs. 41340-25-4D, Etodolac, nitrosylated derivs. 51803-78-2D, Nimesulide, nitrosylated derivs. 52549-17-4D, Pranoprofen, nitrosylated derivs. 53716-49-7D, Carprofen, nitrosylated derivs. 59804-37-4D, Tenoxicam, nitrosylated derivs. 68767-14-6D, Loxoprofen, nitrosylated derivs. 69956-77-0D, CS-670, nitrosylated derivs. 70374-39-9D, Lornoxicam, nitrosylated derivs. 71002-09-0D, Pirazolac, nitrosylated derivs. 71125-38-7D, Meloxicam, nitrosylated derivs. 74103-06-3D, Ketorolac, nitrosylated derivs. 74711-43-6D, Zaltoprofen, nitrosylated derivs. 78499-27-1D, Bermoprofen, nitrosylated derivs. 78967-07-4D, Mofezolac, nitrosylated derivs. 91714-94-2D, Bromfenac, nitrosylated derivs. 114716-16-4D, Pemedolac, nitrosylated derivs. 123653-11-2D, NS-398, nitrosylated derivs. 158205-05-1D, L-745337, nitrosylated derivs. 169590-42-5D, Celecoxib, nitrosylated derivs. **170591-17-0** 174454-51-4 175033-36-0 180200-68-4D, JTE-522, nitrosylated derivs. 181695-72-7D, Valdecoxib, nitrosylated derivs. 220991-20-8D, COX-189, nitrosylated derivs. 287118-96-1 287118-97-2 290335-22-7 302543-76-6 302543-78-8 326850-30-0 410071-14-6 410071-15-7 475561-43-4 612478-30-5 612478-31-6 849015-04-9 849015-07-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

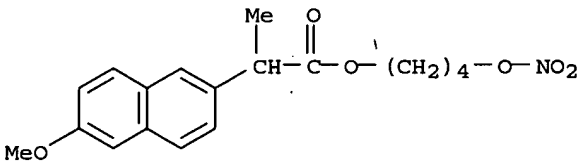
RE

(1) de Clercq, E; MOLECULAR PHARMACOLOGY 1978, V14(3), P422 HCAPLUS
(2) Del Soldato, P; US 5861426 A 1999 HCAPLUS
(3) Fang, X; WO 0145703 A 2001 HCAPLUS
(4) Fiorucci, S; BRITISH JOURNAL OF PHARMACOLOGY 2002, V135(3), P589 HCAPLUS
(5) Garvey, D; WO 03013432 A 2003 HCAPLUS
(6) Khalili, P; EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES 2003, V19(4), P305 HCAPLUS
(7) Nicox Sa; EP 1219306 A 2002 HCAPLUS

IT **170591-17-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrosylated analgesic and/or antiinflammatory drugs having antiviral activity)

RN 170591-17-0 HCAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



L14 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2004:203791 HCAPLUS

DN 140:253349

ED Entered STN: 14 Mar 2004

TI Process for preparing nitrooxyalkyl esters of naproxen and bromonaproxen.

IN Del Soldato, Piero; Santus, Giancarlo; **Benedini, Francesca**

PA **Nicox** S.A., Fr.

SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM C07C201-02
ICS C07C203-04
CC 25-24 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004020384	A1	20040311	WO 2003-EP8698	20030806
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1532098	A1	20050525	EP 2003-747879	20030806
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI IT 2002-MI1861	A	20020829		
WO 2003-EP8698	W	20030806		

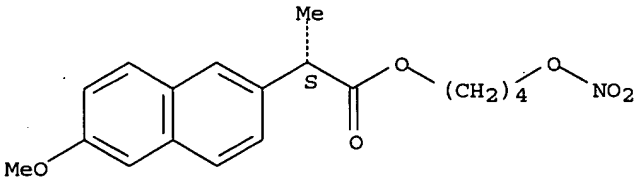
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004020384	ICM	C07C201-02
	ICS	C07C203-04
WO 2004020384	ECLA	C07C201/02; C07C203/04

OS CASREACT 140:253349; MARPAT 140:253349
AB RCO2(CR1R2)m(CR3R4)n(CR5R6)oXp(CR7R8)q(CR9R10)r(CR11R12)sONO2 [R = naproxen, bromonaproxen residue; R1-R12 = H, alkyl, aralkyl; m, n, o, q, r, s = 0-6; p = 0, 1; X = O, S, SO, SO2, NR13, PR13, (substituted) cycloalkylene, arylene, heterocyclylene; R13 = H, alkyl], were prepared by reaction of RCO2Z (R as defined above; Z = H, Li+, Na+, K+, Ca++, Mg++, tetralkylammonium, tetralkylphosphonium) with Y(CR1R2)m(CR3R4)n(CR5R6)oXp(CR7R8)q(CR9R10)r(CR11R12)sONO2 [Y = halo, BF4, SbF6, FSO3, ASO3; A = (substituted) alkyl; other variables as defined above]. Thus, a mixture of naproxen and KHCO3 was heated in DMF at 50-60° for 90 min.; the mixture was cooled to room temperature and treated with KI and 4-bromobutyl nitrate (preparation given) followed by stirring for 25 h to give 73% naproxen 4-nitrooxybutyl ester.
ST nitrooxyalkyl ester naproxen bromonaproxen prepn; methoxynaphthylpropionic acid bromobutyl nitrate esterification reaction
IT Esterification
(preparation of nitrooxyalkyl esters of naproxen and bromonaproxen)
IT 14797-55-8P, Nitrate, preparation
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(esters; preparation of nitrooxyalkyl esters of naproxen and bromonaproxen)
IT **163133-43-5P, (S)-2-(6-Methoxy-2-naphthyl) propanoic acid 4-nitrooxybutyl ester**
669692-80-2P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of nitrooxyalkyl esters of naproxen and bromonaproxen)
IT 68-12-2, Dmf, uses
RL: NUU (Other use, unclassified); USES (Uses)
(preparation of nitrooxyalkyl esters of naproxen and bromonaproxen)
IT 98-59-9, Tosyl chloride 22204-53-1, Naproxen 33036-62-3, 4-Bromobutanol 84236-26-0, (S)-2-(5-Bromo-6-methoxy-2-naphthyl)propanoic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of nitrooxyalkyl esters of naproxen and bromonaproxen)
IT 110798-26-0P, 4-Bromobutyl tosylate 146563-40-8P, 4-Bromobutyl nitrate 669692-75-5P, 4-Nitrooxybutyl p-toluenesulfonate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(preparation of nitrooxyalkyl esters of naproxen and bromonaproxen)
IT 110-86-1, Pyridine, reactions 121-44-8, Triethylamine, reactions
298-14-6, Potassium bicarbonate 7664-93-9, Sulfuric acid, reactions
7681-11-0, Potassium iodide, reactions 7697-37-2, Nitric acid, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(preparation of nitrooxyalkyl esters of naproxen and bromonaproxen)
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Abadi, A; ARCHIV DER PHARMAZIE 2001, V334(3), P104 HCAPLUS
(2) Droux, S; WO 9825918 A 1998 HCAPLUS
(3) Giordano, C; TETRAHEDRON 1989, V45(13), P4243 HCAPLUS
(4) Kawaken Fine Chem Co Ltd; JP 05279359 A 1993 HCAPLUS
(5) Kawashima; JOURNAL OF MEDICINAL CHEMISTRY 1993, V36, P815 HCAPLUS
(6) Nicox Ltd; WO 9509831 A 1995 HCAPLUS
(7) Nicox Sa; WO 0110814 A 2001 HCAPLUS
(8) Ogawa, T; CHEMICAL AND PHARMACEUTICAL BULLETIN 1993, V41(6), P1049 HCAPLUS
IT **163133-43-5P, (S)-2-(6-Methoxy-2-naphthyl) propanoic acid 4-nitrooxybutyl ester**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of nitrooxyalkyl esters of naproxen and bromonaproxen)
RN 163133-43-5 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:2666 HCAPLUS
DN 140:65191
ED Entered STN: 02 Jan 2004
TI Oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability
IN Del Soldato, Piero; Santus, Giancarlo; Macelloni, Cristina
PA **Nicox** S.A., Fr.
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-107
ICS A61K031-216; A61K031-235; A61K031-407; A61K031-426; A61K031-44; A61K031-4164; A61K031-4709
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004000273	A1	20031231	WO 2003-EP6496	20030620

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
EP 1526839 A1 20050504 EP 2003-760660 20030620
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
PRAI IT 2002-MI1392 A 20020625
WO 2003-EP6496 W 20030620

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004000273	ICM	A61K009-107
	ICS	A61K031-216; A61K031-235; A61K031-407; A61K031-426; A61K031-44; A61K031-4164; A61K031-4709
WO 2004000273	ECLA	A61K009/107D; A61K009/14H2; A61K031/216; A61K031/216+M; A61K031/235; A61K031/235+M; A61K031/407; A61K031/407+M; A61K031/4164; A61K031/4164+M; A61K031/426; A61K031/426+M; A61K031/44; A61K031/44+M; A61K031/4709; A61K031/4709+M; A61K047/02

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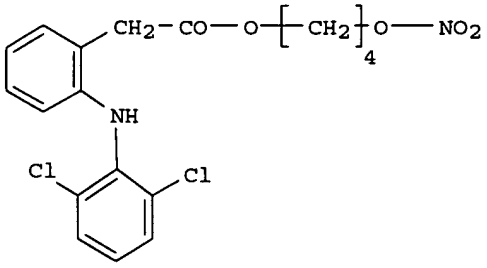

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AB The present invention relates to new pharmaceutical compns. for the administration of liquid drugs in solid oral forms, said compns. comprising one or more active ingredients, one or more surface-active agents and optionally a co-surfactant and/or an absorption enhancer absorbed on a solid inert carrier. An emulsion was prepared containing I 100, Cremophor EL 50, Phospholipon 80H 50, Aerosil 200 100, and Explotab 100 g.

ST oral pharmaceutical liq nitrate ester NSAID

IT Glycerides, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10, ethoxylated; oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)

IT Quaternary ammonium compounds, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkylbenzyldimethyl, chlorides; oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)

IT Drug delivery systems
(capsules; oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)

IT Castor oil
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethoxylated; oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)

IT Anti-inflammatory agents
(nonsteroidal, nitrate esters; oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)

IT Drug bioavailability
Surfactants
(oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)

IT Alcohols, biological studies
Bentonite, biological studies
Clays, biological studies
Glycerides, biological studies
Kaolin, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)

IT Drug delivery systems
(tablets; oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)

IT 56-81-5, Glycerol, biological studies 57-09-0, Cetyltrimethylammonium bromide 57-55-6, Propylene glycol, biological studies 64-17-5, Ethanol, biological studies 67-63-0, Isopropanol, biological studies 67-68-5, Dmso, biological studies 68-12-2, Dmf, biological studies 71-23-8, 1-Propanol, biological studies 71-36-3, 1-Butanol, biological studies 78-83-1, Isobutyl alcohol, biological studies 107-21-1, Ethylene glycol, biological studies 111-90-0 127-19-5, Dimethylacetamide 151-21-3, Sodium lauryl sulfate, biological studies 558-43-0, Isobutylene glycol 577-11-7, Dioctyl sodium sulfosuccinate 593-29-3, Potassium stearate 616-45-5, 2-Pyrrolidone 822-16-2, Sodium stearate 1309-42-8, Magnesium hydroxide 7631-86-9, Silica, biological studies 8044-71-1, Cetrimide 9002-92-0, Polyoxyethylene lauryl ether 9004-34-6, Cellulose, biological studies 9005-25-8, Starch, biological studies 9016-45-9, Polyoxyethylene nonylphenyl ether 12619-70-4, Cyclodextrin 14807-96-6, Talc, biological studies 14987-04-3, Magnesium trisilicate 21645-51-2, Aluminum hydroxide, biological studies 25265-75-2, Butylene glycol 63799-56-4, Labrafac 74791-03-0
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)

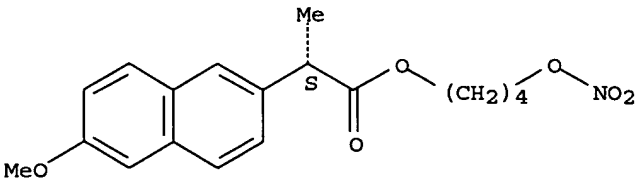
IT 50-53-3, Chlorpromazine, biological studies 54-11-5, Nicotine 55-63-0, Nitroglycerin 77-38-3, Chlorphenoxamine 99-66-1, Valproic acid 104-31-4, Benzonatate 113-92-8, Chlorpheniramine maleate 461-78-9, Chlorphentermine 637-07-0, Clofibrate 156661-01-7 156970-83-1 158836-71-6 **163133-43-5** 164790-48-1 171781-26-3
174454-43-4 174454-49-0 175033-36-0 204633-00-1 301669-93-2
302543-79-9 311336-57-9 311336-59-1 311336-64-8 311336-66-0
352464-58-5 352464-62-1 497818-52-7 569371-19-3 639067-51-9
639067-52-0 639067-53-1 639067-54-2 639067-55-3 639067-56-4
639067-57-5 639067-58-6 639067-59-7 639067-60-0 639067-61-1
639067-62-2 639067-63-3 639067-64-4 639067-65-5 639067-66-6
639067-67-7 639067-68-8 639067-69-9 639067-70-2 639067-71-3
639067-72-4 639067-73-5 639067-75-7
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Astrazeneca Ab; WO 0166087 A 2001 HCAPLUS
(2) Astrazeneca Ab; WO 0166088 A 2001 HCAPLUS
(3) Nicox Sa; WO 0061537 A 2000 HCAPLUS

IT **163133-43-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral pharmaceutical liquid drugs containing nitrate ester NSAIDs having improved bioavailability)

RN 163133-43-5 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:818296 HCAPLUS
DN 139:302040
ED Entered STN: 17 Oct 2003
TI Nitrooxy derivatives of antiinflammatory/analgesic compounds for the treatment of arthritis
IN Del Soldato, Piero
PA Nicox S.A., Fr.
SO PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-616
ICS A61K031-19; A61K031-195; A61K031-165; A61K031-216; A61K031-44; A61K031-40; A61P019-02
CC 1-7 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003084550	A1	20031016	WO 2003-EP3183	20030327
W: AE, AG, AL, AU, BA, BB, BR, BZ, CA, CN, CO, CR, CU, DM, DZ, EC, GD, GE, HR, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, SG, TN, TT, UA, US, UZ, VN, YU, ZA				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1492543	A1	20050105	EP 2003-720377	20030327
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI IT 2002-MI773	A	20020411		
WO 2003-EP3183	W	20030327		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003084550	ICM	A61K031-616
	ICS	A61K031-19; A61K031-195; A61K031-165; A61K031-216; A61K031-44; A61K031-40; A61P019-02
WO 2003084550	ECLA	A61K031/165; A61K031/19; A61K031/195; A61K031/216; A61K031/40; A61K031/44; A61K031/616

OS MARPAT 139:302040
AB Antiinflammatory and/or antiinflammatory/analgesic compds. having the formula A(B)b0(C)c0-N(O)s [A contains radical of nonsteroidal antiinflammatory or nonsteroidal antiinflammatory/analgesic drug; B, C = bivalent linking group; s = 1, 2; b0, c0 = 0, 1 (with proviso)], and salts thereof, are disclosed for use in the treatment of arthritis.
ST antiinflammatory analgesic nitrooxy deriv arthritis treatment
IT Lymphocyte
(IL-6 and TGFβ release; nitrooxy derivs. of antiinflammatory/analgesic compds. for treatment of arthritis)
IT Monocyte
(IL-6 release; nitrooxy derivs. of antiinflammatory/analgesic compds. for treatment of arthritis)
IT Transforming growth factor receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TGF-β receptor, type II; nitrooxy derivs. of
antiinflammatory/analgesic compds. for treatment of arthritis)
IT Chondrocyte
(TGFβ1 production; nitrooxy derivs. of antiinflammatory/analgesic
compds. for treatment of arthritis)
IT Alcohols, biological studies
Carboxylic acids, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(derivs.; nitrooxy derivs. of antiinflammatory/analgesic compds. for
treatment of arthritis)
IT Carboxylic acids, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(hydroxy, derivs.; nitrooxy derivs. of antiinflammatory/analgesic
compds. for treatment of arthritis)
IT Interleukin 6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(monocyte release of; nitrooxy derivs. of antiinflammatory/analgesic
compds. for treatment of arthritis)
IT Analgesics
Antiarthritics
Arthritis
Cell proliferation
Drug toxicity
Hepatotoxicity
Human
Liver
(nitrooxy derivs. of antiinflammatory/analgesic compds. for treatment
of arthritis)
IT Proteoglycans, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nitrooxy derivs. of antiinflammatory/analgesic compds. for treatment
of arthritis)
IT Amino acids, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(nitrooxy derivs. of antiinflammatory/analgesic compds. for treatment
of arthritis)
IT Anti-inflammatory agents
(nonsteroidal; nitrooxy derivs. of antiinflammatory/analgesic compds.
for treatment of arthritis)
IT Drug delivery systems
(oral; nitrooxy derivs. of antiinflammatory/analgesic compds. for
treatment of arthritis)
IT Drug delivery systems
(parenterals; nitrooxy derivs. of antiinflammatory/analgesic compds.
for treatment of arthritis)
IT Alcohols, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(polyhydric, derivs.; nitrooxy derivs. of antiinflammatory/analgesic
compds. for treatment of arthritis)
IT Drug delivery systems
(topical; nitrooxy derivs. of antiinflammatory/analgesic compds. for
treatment of arthritis)
IT Liver
(toxicity; nitrooxy derivs. of antiinflammatory/analgesic compds. for
treatment of arthritis)
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-, lymphocyte release of; nitrooxy derivs. of
antiinflammatory/analgesic compds. for treatment of arthritis)
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(β1-, chondrocyte production; nitrooxy derivs. of antiinflammatory/analgesic compds. for treatment of arthritis)

IT 50-78-2D, Acetylsalicylic acid, derivs. 50-81-7D, Ascorbic acid, derivs. 52-67-5D, Penicillamine, derivs. 52-90-4D, L-Cysteine, derivs. 53-86-1D, Indomethacin, derivs. 57-50-1D, Saccharose, derivs. 60-00-4D, Edetic acid, derivs. 69-72-7D, Salicylic acid, derivs. 70-18-8D, Glutathione, derivs. 77-92-9D, Citric acid, derivs. 89-65-6D, Isoascorbic acid, derivs. 103-90-2D, Paracetamol, derivs. 110-17-8D, Fumaric acid, derivs. 111-17-1D, 3,3'-Thiodipropionic acid, derivs. 117-39-5D, Quercetin, derivs. 120-05-8D, Sulphuretin, derivs. 121-34-6D, Vanillic acid, derivs. 121-79-9D, Propyl gallate, derivs. 123-31-9D, Hydroquinone, derivs. 149-91-7D, Gallic acid, derivs. 154-23-4D, Catechin, derivs. 305-84-0D, L-Carnosine, derivs. 315-30-0D, Allopurinol, derivs. 331-39-5D, Caffeic acid, derivs. 458-35-5D, Coniferyl alcohol, derivs. 490-79-9D, Gentisic acid, derivs. 500-38-9D, Nordihydroguaiaretic acid, derivs. 501-94-0D, derivs. 520-18-3D, Kempferol, derivs. 526-84-1D, Dihydroxymaleic acid, derivs. 533-73-3D, Hydroxyhydroquinone, derivs. 584-85-0D, Anserine, derivs. 616-91-1D, N-Acetylcysteine, derivs. 824-46-4D, derivs. 1078-61-1D, Dihydrocaffeic acid, derivs. 1135-24-6D, Ferulic acid, derivs. 1464-42-2D, Selenomethionine, derivs. 3411-58-3D, L-Cysteine ethyl ester, derivs. 3538-61-2D, derivs. 3614-08-2D, Selenocysteine, derivs. 3690-05-9D, p-Cumaric alcohol, derivs. 5104-49-4D, Flurbiprofen, derivs. 7400-08-0D, p-Cumaric acid, derivs. 15537-71-0D, N-Acetylpenicillamine, derivs. 15687-27-1D, Ibuprofen, derivs. 21611-48-3D, derivs. 22071-15-4D, Ketoprofen, derivs. 26171-23-3D, Tolmetin, derivs. 31842-01-0D, Indoprofen, derivs. 33005-95-7D, Tiaprofenic acid, derivs. 36211-20-8D, Penicillamine ethyl ester, derivs. 36322-90-4D, Piroxicam, derivs. 36330-85-5D, Fenbufen, derivs. 38194-50-2D, Sulindac, derivs. 38677-85-9D, Flunixin, derivs. 41340-25-4D, Etodolac, derivs. 42924-53-8D, Nabumetone, derivs. 52549-17-4D, Pranoprofen, derivs. 53716-49-7D, Carprofen, derivs. 59587-09-6D, N-Acetylcysteine ethyl ester, derivs. 59804-37-4D, Tenoxicam, derivs. 60654-26-4D, L-Cysteine propyl ester, derivs. 63147-28-4D, 3,5-Di-tert-butyl-4-hydroxybenzylthioglycolate, derivs. 67607-91-4D, derivs. 68767-14-6D, Loxoprofen, derivs. 69956-77-0D, derivs. 70374-39-9D, Lornoxicam, derivs. 71002-09-0D, Pirazolac, derivs. 71125-38-7D, Meloxicam, derivs. 74103-06-3D, Ketorolac, derivs. 74711-43-6D, Zaltoprofen, derivs. 78499-27-1D, Bermoprofen, derivs. 78967-07-4D, Mofezolac, derivs. 91714-94-2D, Bromfenac, derivs. 92614-59-0D, Glutathione ethyl ester, derivs. 97473-82-0D, derivs. 99464-64-9D, Ampiroxicam, derivs. 156661-01-7 156970-83-1 158836-71-6 164790-48-1 **170591-17-0** 174454-43-4 175033-36-0 204268-63-3 290335-36-3 302543-75-5 311336-58-0 311336-60-4 311336-61-5 326850-30-0 497818-52-7 497818-53-8 497818-54-9 612478-19-0D, derivs. 612478-20-3D, derivs. 612478-21-4D, derivs. 612478-22-5D, derivs. 612478-23-6D, derivs. 612478-24-7D, derivs. 612478-25-8D, derivs. 612478-26-9D, derivs. 612478-27-0D, derivs. 612478-28-1 612478-29-2 612478-30-5 612478-31-6 612478-32-7

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(nitrooxy derivs. of antiinflammatory/analgesic compds. for treatment of arthritis)

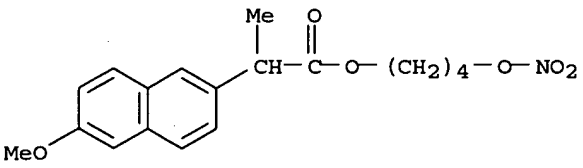
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Armour, K; ARTHRITIS AND RHEUMATISM 2001, V44(9), P2185 HCAPLUS
(2) Burgaud; DRUGS OF THE FUTURE 1999, V24(8), P858 HCAPLUS
(3) Burgaud, J; CURRENT PHARMACEUTICAL DESIGN 2002, V8(3), P201 HCAPLUS
(4) Cassella Ag; DE 4420523 A 1995 HCAPLUS
(5) Cuzzolin, L; PHARMACOLOGICAL RESEARCH 1995, V31(1), P61 HCAPLUS
(6) Del Soldato, P; US 5621000 A 1997 HCAPLUS
(7) Del Soldato, P; US 5861426 A 1999 HCAPLUS
(8) Del Soldato, P; TRENDS IN PHARMACOLOGICAL SCIENCES 1999, V20(8), P319 HCAPLUS
(9) Fiorucci, S; MEDICAL SCIENCE SYMPOSIA SERIES 2001, V16, P171 HCAPLUS
(10) Hof van 'T, R; CALCIFIED TISSUE INTERNATIONAL 1999, V64(SUPPL 1), PS59

(11) Kato, S; DIGESTIVE DISEASES AND SCIENCES 2001, V46(8), P1690 HCAPLUS
(12) Paul-Clark, M; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA 2002, V99(3), P1677 HCAPLUS
(13) Soldato Del, P; INFLAMMOPHARMACOLOGY 1996, V4(2), P181

IT **170591-17-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrooxy derivs. of antiinflammatory/analgesic compds. for treatment of arthritis)
RN 170591-17-0 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



L14 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:133017 HCAPLUS
DN 138:163547
ED Entered STN: 21 Feb 2003
TI Nitrooxy compounds for treatment of vasculopaties
IN Del Soldato, Piero
PA **Nicox** S.A., Fr.
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-21
ICS A61K031-435; A61P007-00; A61P009-00
CC 1-8 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003013499	A2	20030220	WO 2002-EP8374	20020726
WO 2003013499	A3	20031231		

W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, RO, SG, SI, SK, TN, TR, TT, UA, US, UZ, VN, YU, ZA
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

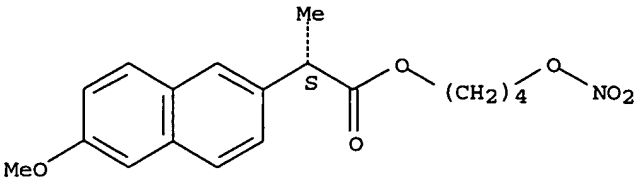
PRAI IT 2001-MI1744 A 20010809
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003013499	ICM	A61K031-21
	ICS	A61K031-435; A61P007-00; A61P009-00
WO 2003013499	ECLA	A61K031/21; A61K031/435+A

OS MARPAT 138:163547
AB The invention discloses the use for vasculopathy treatment of nitrooxy compds. (Markush included), or salts thereof. Compds. of the invention include e.g. 2-fluoro-α-methyl-4-diphenylacetic acid (4-nitrooxy)butyl ester (NO-flurbiprofen).
ST nitrooxy ester drug vasculopathy; flurbiprofen nitrooxy deriv vasculopathy drug
IT Carboxylic acids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(hydroxy; nitrooxy compds. for treatment of vasculopaties)
IT Blood vessel, disease
Cardiovascular agents
(nitrooxy compds. for treatment of vasculopaties)
IT Amino acids, biological studies
Carboxylic acids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nitrooxy compds. for treatment of vasculopaties)
IT Drug delivery systems
(oral; nitrooxy compds. for treatment of vasculopaties)
IT Drug delivery systems
(parenterals; nitrooxy compds. for treatment of vasculopaties)
IT Alcohols, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(polyhydric, aromatic and heterocyclic; nitrooxy compds. for treatment of vasculopaties)
IT Artery, disease
(restenosis; nitrooxy compds. for treatment of vasculopaties)
IT 290335-35-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(46nitrooxy compds. for treatment of vasculopaties)
IT 50-81-7, Ascorbic acid, biological studies 52-67-5, Penicillamine 52-90-4, Cysteine, biological studies 57-50-1, Saccharose, biological studies 60-00-4, Edetic acid, biological studies 70-18-8D, Glutathione, esters 77-92-9, Citric acid, biological studies 80-72-8, Reductic acid 89-65-6, Isoascorbic acid 110-17-8, Fumaric acid, biological studies 111-17-1, 3,3'-Thiodipropionic acid 117-39-5, Quercetin 120-05-8, Sulphuretin 121-34-6, Vanillic acid 121-79-9, Propyl gallate 123-31-9, Hydroquinone, biological studies 149-91-7, Gallic acid, biological studies 154-23-4, Catechin 303-45-7, Gossypol 305-84-0, L-Carnosine 315-30-0, Allopurinol 331-39-5, Caffeic acid 458-35-5, Coniferyl alcohol 490-79-9, Gentisic acid 500-38-9, Nordihydroguaiaretic acid 501-94-0 520-18-3, Kaempferol 526-84-1, Dihydroxymaleic acid 533-73-3, Hydroxyhydroquinone 584-85-0, Anserine 616-91-1, N-Acetylcysteine 824-46-4, Methoxyhydroquinone 1078-61-1, Dihydrocaffeic acid 1135-24-6, Ferulic acid 1464-42-2, Selenomethionine 3614-08-2, Selenocysteine 3690-05-9, p-Cumaric alcohol 7400-08-0, p-Cumaric acid 15537-71-0, N-Acetylpenicillamine 63147-28-4, 3,5-Di-tert-butyl-4-hydroxybenzylthioglycolate 92614-59-0, Glutathione ethyl ester 97451-46-2, Glutathione isopropyl ester
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nitrooxy compds. for treatment of vasculopaties)
IT 5104-49-4, Flurbiprofen 164790-48-1
RL: PAC (Pharmacological activity); BIOL (Biological study)
(nitrooxy compds. for treatment of vasculopaties)
IT 5104-49-4D, Flurbiprofen, nitrooxy derivs. 15307-86-5D, Diclofenac, nitrooxy derivs. 22204-53-1D, Naproxen, nitrooxy derivs. 156661-01-7 158836-71-6 **163133-43-5** 290335-26-1 302543-75-5 302543-79-9 410071-57-7 475561-43-4 497818-52-7 497818-53-8 497818-54-9 497818-55-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrooxy compds. for treatment of vasculopaties)
IT **163133-43-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrooxy compds. for treatment of vasculopaties)
RN 163133-43-5 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:115100 HCAPLUS
DN 134:178355
ED Entered STN: 15 Feb 2001
TI Process for the preparation of naproxene nitroxyalkyl esters
IN **Benedini, Francesca; Oldani, Erminio; Castaldi, Graziano**; Tarquini, Antonio
PA **Nicox** S.A., Fr.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C203-04
CC 25-24 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001010814	A1	20010215	WO 2000-EP7222	20000727
	W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2380116	AA	20010215	CA 2000-2380116	20000727
	EP 1200386	A1	20020502	EP 2000-951456	20000727
	EP 1200386	B1	20031001		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	TR 200200290	T2	20020521	TR 2002-200200290	20000727
	BR 2000012915	A	20020604	BR 2000-12915	20000727
	JP 2003506425	T2	20030218	JP 2001-515282	20000727
	AT 251109	E	20031015	AT 2000-951456	20000727
	EP 1384707	A1	20040128	EP 2003-102132	20000727
	EP 1384707	B1	20050608		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, FI, CY				
	PT 1200386	T	20040227	PT 2000-951456	20000727
	ES 2208390	T3	20040616	ES 2000-951456	20000727
	AU 778694	B2	20041216	AU 2000-64385	20000727
	RU 2248348	C2	20050320	RU 2002-102860	20000727
	ZA 2002000478	A	20030818	ZA 2002-478	20020118
	US 6700011	B1	20040302	US 2002-31412	20020118
	NO 2002000515	A	20020201	NO 2002-515	20020201
	ZA 2003004525	A	20040211	ZA 2003-4525	20030610
	US 2005119339	A1	20050602	US 2003-625558	20030724
PRAI	IT 1999-MI1753	A	19990804		
	EP 2000-951456	A3	20000727		
	WO 2000-EP7222	W	20000727		
	US 2002-31412	A3	20020118		

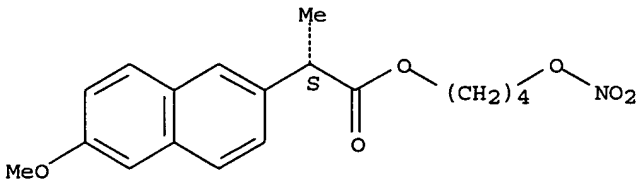
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001010814	ICM	C07C203-04

Search done by Noble Jarrell

WO 2001010814 ECLA C07C203/04
EP 1384707 ECLA C07C203/04
US 6700011 NCL 558/482.000
ECLA C07C203/04
US 2005119339 NCL 514/510.000; 558/482.000
OS CASREACT 134:178355; MARPAT 134:178355
AB A process for obtaining nitroxyalkyl esters of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid having an enantiomeric excess higher than or equal to 95 %, preferably higher than or equal to 98 %, was characterized in that a halide of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid of formula A-Hal, wherein A is the acid acyl residue, is reacted in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO2, wherein Y is a C2-C20 alkylene or a cycloalkylene from 3 to 8 carbon atoms, or an alkylene as defined containing a cycloalkylene as defined, in the presence of an inorg. base. E.g., to a solution of 4-nitroxybutan-1-ol and K2CO3 in dichloromethane is added 2-(S)-(6-methoxy-2-naphthyl)propanoic acid chloride. to give the 4-nitroxybutyl ester of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (85%, ee 98%).
ST naproxene nitroxyalkyl ester prepn; naproxen nitroxyalkyl ester prepn
IT **163133-43-5P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of naproxene nitroxyalkyl esters)
IT 22204-53-1, Naproxen 22911-39-3 51091-84-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of naproxene nitroxyalkyl esters)
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Hoechst Marion Roussel Inc; FR 2757159 A 1998 HCAPLUS
(2) Italfarmaco Spa; WO 9201668 A 1992 HCAPLUS
(3) Nicox Ltd; WO 9509831 A 1995 HCAPLUS
(4) Nicox Ltd; WO 9530641 A 1995 HCAPLUS
(5) Nicox Sa; WO 9716405 A 1997 HCAPLUS
IT **163133-43-5P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of naproxene nitroxyalkyl esters)
RN 163133-43-5 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:594647 HCAPLUS
DN 127:257627
ED Entered STN: 17 Sep 1997
TI Nitric oxide donors capable of reducing renal, gastrointestinal, or respiratory drug toxicity
IN Del Soldato, Piero
PA Nicox S.A., Fr.; Del Soldato, Piero
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K045-06

CC 1-8 (Pharmacology)
Section cross-reference(s): 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9731654	A1	19970904	WO 1997-EP873	19970224
	W: AL, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2247848	AA	19970904	CA 1997-2247848	19970224
	AU 9720924	A1	19970916	AU 1997-20924	19970224
	AU 706591	B2	19990617		
	EP 904110	A1	19990331	EP 1997-906115	19970224
	EP 904110	B1	20020724		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, SI, LT, FI				
	BR 9707739	A	19990727	BR 1997-7739	19970224
	JP 2000506133	T2	20000523	JP 1997-530576	19970224
	EP 1221326	A2	20020710	EP 2002-8079	19970224
	EP 1221326	A3	20040114		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, SI, LT, FI				
	AT 220920	E	20020815	AT 1997-906115	19970224
	RU 2192247	C2	20021110	RU 1998-117618	19970224
	PT 904110	T	20021231	PT 1997-906115	19970224
	ES 2180938	T3	20030216	ES 1997-906115	19970224
	US 2004242651	A1	20041202	US 2004-885121	20040707
PRAI	IT 1996-MI352	A	19960226		
	EP 1997-906115	A3	19970224		
	WO 1997-EP873	W	19970224		
	US 1998-125878	B1	19980826		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9731654	ICM	A61K045-06
EP 1221326	ECLA	A61K045/06
US 2004242651	NCL	514/352.000; 514/509.000
	ECLA	A61K045/06

AB Organic compds. containing the -ONO2 function, or inorg. çompds. containing the -NO group, or compns. comprising these compds., are used to reduce the toxicity caused by drugs to the gastrointestinal, respiratory, and/or renal apparatus, the compds. being characterized in that they are nitric oxide (NO) donors, i.e. when they are put into contact in vitro with cells of the vasal endothelium or platelets.

ST nitric oxide donor drug toxicity redn; kidney drug toxicity NO donor; respiratory tract drug toxicity NO donor; gastrointestinal tract drug toxicity NO donor

IT Steroids, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiinflammatory; nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT Toxicity
(drug; nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT Blood vessel
(endothelium; nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT Antiarthritics
Anticoagulants
Antitumor agents
Antiviral agents

Cardiovascular agents
Digestive tract
Immunosuppressants
Kidney
Platelet (blood)
Respiratory tract
(nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT Antibiotics
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT Anti-inflammatory agents
(nonsteroidal; nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT Drug delivery systems
(oral; nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT Drug delivery systems
(parenterals; nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT Anti-inflammatory agents
(steroidal; nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT Drug delivery systems
(transdermal; nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT 9015-82-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT 50-02-2, Dexamethasone 50-78-2, Aspirin 51-21-8, 5-Fluorouracil 53-06-5, Cortisone 53-86-1, Indomethacin 61-68-7, Mefenamic acid 83-43-2, Methylprednisolone 530-78-9, Flufenamic acid 1403-66-3, Gentamicin 4394-00-7, Niflumic acid 15307-86-5, Diclofenac 15663-27-1, Cisplatin 15687-27-1, Ibuprofen 22071-15-4, Ketoprofen 22204-53-1, Naproxen 26839-75-8, Timolol 29122-68-7, Atenolol 38677-85-9, Flunixin 51384-51-1, Metoprolol 59277-89-3, Acyclovir 62571-86-2, Captopril 74103-06-3, Ketorolac 75847-73-3, Enalapril 79217-60-0, Cyclosporin 85721-33-1, Ciprofloxacin
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT 55-63-0 78-11-5, Pentaerythritol tetranitrate 588-42-1, Trolnitratephosphate 1607-17-6, Pentrinitrol 2612-33-1, Clonitrate 2921-92-8, Propatyl nitrate 7297-25-8, Erythrityltetranitrate 14402-89-2, Sodium nitroprusside 15078-28-1, Nitroprusside 15825-70-4, Mannitol hexanitrate 65141-46-0, Nicorandil 163133-43-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT 7665-99-8, CGMP
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

IT 10102-43-9, Nitric oxide, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(nitric oxide donors for reducing renal, gastrointestinal, or

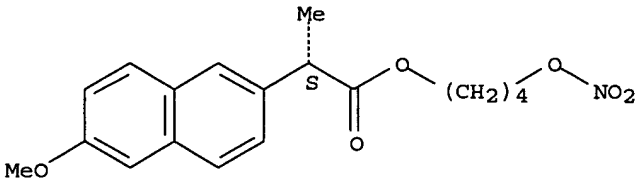
respiratory drug toxicity)

IT 163133-43-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide donors for reducing renal, gastrointestinal, or respiratory drug toxicity)

RN 163133-43-5 HCAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1995:667266 HCAPLUS

DN 123:82961

ED Entered STN: 13 Jul 1995

TI Preparation of organic nitrate esters having antiinflammatory and/or analgesic activity

IN Del Soldato, Piero

PA Nicox Ltd., Ire.

SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM C07C203-04
ICS C07D487-04; C07D209-28; A61K031-40; A61K031-405; A61K031-21

ICI C07D487-04, C07D209-00

CC 25-24 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 23

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9509831	A1	19950413	WO 1994-EP3182	19940923
	W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN				
	RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	GB 2283238	A1	19950503	GB 1993-20599	19931006
	GB 2283238	B2	19971126		
	CA 2173582	AA	19950413	CA 1994-2173582	19940923
	AU 9478092	A1	19950501	AU 1994-78092	19940923
	AU 678063	B2	19970515		
	EP 722434	A1	19960724	EP 1994-928801	19940923
	EP 722434	B1	19980729		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
	HU 74446	A2	19961230	HU 1996-874	19940923
	HU 218923	B	20001228		
	BR 9407749	A	19970212	BR 1994-7749	19940923
	JP 09503214	T2	19970331	JP 1994-510585	19940923
	AT 168986	E	19980815	AT 1994-928801	19940923
	ES 2120070	T3	19981016	ES 1994-928801	19940923
	RU 2136653	C1	19990910	RU 1996-108907	19940923
	US 5700947	A	19971223	US 1996-624508	19960405

	US 5780495	A	19980714	US 1997-902570	19970729
PRAI	GB 1993-20599	A	19931006		
	IT 1994-MI916	A	19940510		
	WO 1994-EP3182	W	19940923		
	US 1996-624508	A3	19960405		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9509831	ICM	C07C203-04
	ICS	C07D487-04; C07D209-28; A61K031-40; A61K031-405; A61K031-21
	ICI	C07D487-04, C07D209-00
WO 9509831	ECLA	C07C203/04; C07D209/28; C07D487/04+209C+209C+2
GB 2283238	ECLA	C07C203/04; C07D209/28; C07D487/04+209C+209C+2
US 5700947	NCL	548/491.000; 548/576.000; 558/482.000; 558/483.000
	ECLA	C07C203/04
US 5780495	NCL	514/413.000; 514/419.000; 548/453.000; 548/491.000
	ECLA	C07C203/04; C07D209/28; C07D487/04+209C+209C+2

OS CASREACT 123:82961; MARPAT 123:82961

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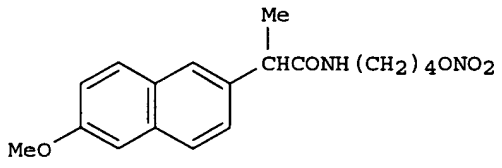

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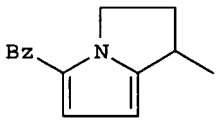
Q1=



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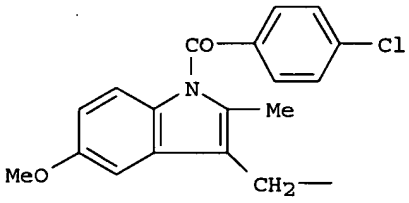


AB The title compds. MCOY[C(A)(B)]nONO2 [A, B = H, (un)branched alkyl; M = Q1, Q2, 2-(6-methoxy)naphthyl, etc.; n = 1-10], useful as analgesics, antiinflammatory agents, and blood platelet aggregation inhibitors, are prepared Thus, 2-(6-methoxy-2-naphthyl)propionic acid was converted into its Na carboxylate salt with NaOEt, the salt condensed with 1-bromo-4-chlorobutane, and the 4-chlorobutyl 2-(6-methoxy-2-naphthyl)propionate intermediate nitrated by reaction with AgNO3, producing the 4-nitratobutyl ester, II.

ST nitratobutyl methoxynaphthylpropionate prepn analgesic; antiinflammatory prepn nitratobutyl methoxynaphthylpropionate

IT Analgesics
Blood platelet aggregation inhibitors
Inflammation inhibitors
(organic nitrate esters)

IT 164790-47-0P 164790-48-1P 164790-49-2P **170591-17-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of organic nitrate esters having antiinflammatory and/or analgesic activity)

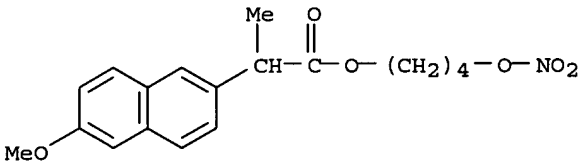
IT 110-52-1, 1,4-Dibromobutane 1074-82-4, Potassium phthalimide 6940-78-9, 1-Bromo-4-chlorobutane 7761-88-8, Silver nitrate, reactions 7789-60-8, Phosphorous tribromide 23981-80-8, 2-(6-Methoxy-2-

naphthyl)propionic acid 74103-06-3, Ketorolac
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of organic nitrate esters having antiinflammatory and/or analgesic activity from)

IT 5394-18-3P 38835-18-6P, 2-(6-Methoxy-2-naphthyl)propionyl chloride
55577-80-5P, Sodium 2-(6-methoxy-2-naphthyl)propionate 164790-50-5P
164790-51-6P 164790-52-7P 164790-53-8P 164790-54-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of organic nitrate esters having antiinflammatory and/or analgesic activity from)

IT **170591-17-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of organic nitrate esters having antiinflammatory and/or analgesic activity)

RN 170591-17-0 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



=> d all hitstr l17 tot

L17 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:676579 HCAPLUS
DN 135:231708
ED Entered STN: 14 Sep 2001
TI New self emulsifying drug delivery system
IN Holmberg, Christina; Siekmann, Britta
PA AstraZeneca AB, Swed.
SO PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-113
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001066088	A1	20010913	WO 2001-SE467	20010306 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2401498	AA	20010913	CA 2001-2401498	20010306 <--
EP 1267832	A1	20030102	EP 2001-910305	20010306 <--
EP 1267832	B1	20040602		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001009014	A	20030603	BR 2001-9014	20010306 <--

JP 2003525894	T2	20030902	JP 2001-564741	20010306 <--
EE 200200500	A	20040216	EE 2002-500	20010306 <--
AT 268162	E	20040615	AT 2001-910305	20010306 <--
NZ 521009	A	20040625	NZ 2001-521009	20010306 <--
PT 1267832	T	20040930	PT 2001-910305	20010306 <--
ES 2220728	T3	20041216	ES 2001-1910305	20010306 <--
ZA 2002006740	A	20031124	ZA 2002-6740	20020822 <--
US 2003161846	A1	20030828	US 2002-220791	20020905 <--
NO 2002004272	A	20021105	NO 2002-4272	20020906 <--
HK 1050632	A1	20050318	HK 2003-102781	20030416 <--
PRAI SE 2000-773	A	20000308 <--		
WO 2001-SE467	W	20010306		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001066088	ICM	A61K009-113
WO 2001066088	ECLA	A61K009/48H6; A61K009/48H4; A61K009/50M; A61K031/21; A61K031/215L5; A61K031/216; A61K031/407; A61K045/06 <--
US 2003161846	NCL	424/400.000; 514/448.000; 514/509.000
	ECLA	A61K009/48H4; A61K009/48H6; A61K009/50M; A61K031/21; A61K031/215L5; A61K031/216; A61K031/407; A61K045/06 <--

OS MARPAT 135:231708

AB The present invention claims and discloses a pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising: 1 or more NO-releasing NSAID(s), 1 or more surfactants, optionally an addnl. oil or semi-solid fat. The composition forms an in-situ oil-in-water emulsion upon contact with gastrointestinal fluids. The composition may optionally also comprise 1 or more short-chain alcs. Also within the scope of the invention is a combination with a proton pump inhibitor. The pharmaceutical composition is useful in the treatment of pain and inflammation. Further within the scope of the invention is kit comprising a pharmaceutical composition according to the invention in a unit dosage form, in combination with a proton pump inhibitor, and the proton pump inhibitor is enteric coated. Thus, a semisolid formulation contained a NO-releasing NSAID 750, Pluronic F127 450, and omeprazole 20 g.

ST self emulsifying drug delivery; naproxen ester emulsifying drug delivery; NSAID oil surfactant drug delivery emulsifying

IT Glycerides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C16-18; self emulsifying drug delivery system)

IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(block; self emulsifying drug delivery system)

IT Drug delivery systems
(capsules; self emulsifying drug delivery system)

IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(esters; self emulsifying drug delivery system)

IT Castor oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethoxylated; self emulsifying drug delivery system)

IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fish; self emulsifying drug delivery system)

IT Drug delivery systems
(liqs.; self emulsifying drug delivery system)

IT Drug delivery systems
(lozenges; self emulsifying drug delivery system)

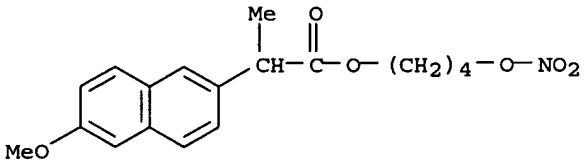
IT Surfactants
(nonionic; self emulsifying drug delivery system)

IT Anti-inflammatory agents
(nonsteroidal; self emulsifying drug delivery system)

IT Drug delivery systems
(pellets, enteric-coated; self emulsifying drug delivery system)

IT Ampuls
Intestinal juice

Surfactants
(self emulsifying drug delivery system)
IT Castor oil
Coconut oil
Corn oil
Diglycerides
Fats and Glyceridic oils, biological studies
Glycerides, biological studies
Monoglycerides
Polyoxyalkylenes, biological studies
Rape oil
Safflower oil
Soybean oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self emulsifying drug delivery system)
IT Drug delivery systems
(semisolid; self emulsifying drug delivery system)
IT Alcohols, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(short-chain; self emulsifying drug delivery system)
IT Drug delivery systems
(tablets, chewable; self emulsifying drug delivery system)
IT Drug delivery systems
(tablets, enteric-coated; self emulsifying drug delivery system)
IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vegetable; self emulsifying drug delivery system)
IT 9000-83-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proton-translocating, inhibitors; self emulsifying drug delivery system)
IT 56-81-5, Glycerol, biological studies 57-55-6, Propylene glycol, biological studies 64-17-5, Ethanol, biological studies 151-21-3, SDS, biological studies 1338-39-2, Sorbitan monolaurate 25322-68-3, Polyethylene glycol 25322-68-3D, Polyethylene glycol, esters 73590-58-6, Omeprazole 73590-58-6D, Omeprazole, salts 95382-33-5, Omeprazole magnesium 102625-70-7, Pantoprazole 103577-45-3, Lansoprazole 104340-86-5, Leminoprazole 106392-12-5, Pluronic 110617-70-4, Poloxamine 111371-26-7 112869-03-1 113712-98-4 116091-80-6 117976-90-6, Pariprazole 119141-88-7, (S)-Omeprazole 119141-88-7D, (S)-Omeprazole, salts 136177-53-2 156661-01-7 156970-83-1 164790-48-1 **170591-17-0** 174454-43-4 174454-51-4 174573-32-1 311336-57-9 311336-58-0 311336-59-1 311336-60-4 311336-61-5 311336-62-6 311336-63-7 311336-64-8 311336-65-9 311336-66-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self emulsifying drug delivery system)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Elan Corporation Plc; WO 9956727 A2 1999 HCAPLUS
(2) Gattefosse S A; WO 9508983 A1 1995 HCAPLUS
(3) Nicox Limited; WO 9509831 A1 1995 HCAPLUS
IT **170591-17-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self emulsifying drug delivery system)
RN 170591-17-0 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



L17 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:676578 HCAPLUS
DN 135:231707
ED Entered STN: 14 Sep 2001
TI New self emulsifying drug delivery system
IN Holmberg, Christina; Siekmann, Britta
PA AstraZeneca AB, Swed.
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-113
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2001066087	A1	20010913	WO 2001-SE466	20010306	<--
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
	CA 2401857	AA	20010913	CA 2001-2401857	20010306	<--
	EP 1267831	A1	20030102	EP 2001-910304	20010306	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
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	EE 200200483	A	20040216	EE 2002-483	20010306	<--
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	US 2003077303	A1	20030424	US 2002-221079	20020905	
PRAI	SE 2000-774	A	20000308	<--		
	WO 2001-SE466	W	20010306			

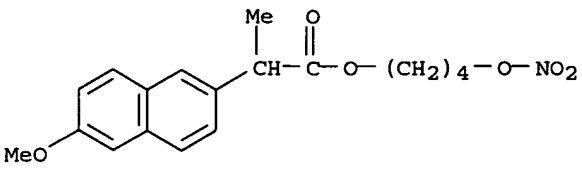
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2001066087	ICM	A61K009-113	
WO 2001066087	ECLA	A61K009/48H6; A61K031/216	<--
US 2003077303	NCL	424/400.000; 514/509.000; 514/510.000	

AB The present invention claims and discloses a pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising a nitro-group-containing naproxen ester (I) , 1 or more surfactants, an oil or a semi-solid fat; the composition forming an in-situ oil-in-water emulsion upon contact with aqueous media such as gastrointestinal fluids. The composition may optionally also comprise 1 or more short-chain alcs. The pharmaceutical composition is useful in the treatment of pain and inflammation. Thus, a semisolid formulation contained I 3, Pluronic L 127 0.843, sorbitan monolaurate 0.282, and propylene glycol 0.375 g.
ST self emulsifying drug delivery; surfactant alc naproxen ester oil emulsifying
IT Glycerides, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C16-18; self emulsifying drug delivery system)
IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(block; self emulsifying drug delivery system)
IT Drug delivery systems
(capsules; self emulsifying drug delivery system)
IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(esters; self emulsifying drug delivery system)
IT Castor oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethoxylated, Cremophor EL; self emulsifying drug delivery system)
IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fish; self emulsifying drug delivery system)
IT Drug delivery systems
(lozenges; self emulsifying drug delivery system)
IT Surfactants
(nonionic; self emulsifying drug delivery system)
IT Ampuls
Analgesics
Anti-inflammatory agents
Intestinal juice
Surfactants
(self emulsifying drug delivery system)
IT Castor oil
Coconut oil
Corn oil
Diglycerides
Fats and Glyceridic oils, biological studies
Glycerides, biological studies
Monoglycerides
Rape oil
Soybean oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self emulsifying drug delivery system)
IT Drug delivery systems
(semisolid; self emulsifying drug delivery system)
IT Alcohols, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(short-chain; self emulsifying drug delivery system)
IT Drug delivery systems
(tablets, chewable; self emulsifying drug delivery system)
IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vegetable; self emulsifying drug delivery system)
IT 110617-70-4, Poloxamine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Poloxamine 1107; self emulsifying drug delivery system)
IT 56-81-5, Glycerol, biological studies 57-55-6, Propylene glycol, biological studies 64-17-5, Ethanol, biological studies 151-21-3, Sodium dodecyl sulfate, biological studies 1338-39-2, Sorbitan monolaurate 25322-68-3D, Polyethylene glycol, esters 106392-12-5, Poloxamer 107628-12-6, Polyglycol BM 45 **170591-17-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self emulsifying drug delivery system)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Elan Corporation Plc; WO 9956727 A2 1999 HCAPLUS
(2) Gattefosse S A; WO 9508983 A1 1995 HCAPLUS
(3) Nicox Limited; WO 9509831 A1 1995 HCAPLUS
IT **170591-17-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self emulsifying drug delivery system)
RN 170591-17-0 HCAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



L17 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:1455 HCAPLUS
DN 135:70874
ED Entered STN: 01 Jan 2001
TI Gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs
AU Brzozowski, T.; Konturek, P. Ch.; Konturek, S. J.; Sliwowski, Z.; Drozdowicz, D.; Kwiecien, S.; Pajdo, R.; Ptak, A.; Pawlik, M.; Hahn, E.
CS Department of Physiology, Jagiellonian University School of Medicine, Krakow, 31-531, Pol.
SO Digestive and Liver Disease (2000), 32(7), 583-594
CODEN: DLDIFK
PB Pacini Editore
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Background & Aim. New class of nitric oxide-releasing non-steroidal anti-inflammatory drugs was shown to inhibit cyclooxygenase and prostaglandin generation without causing mucosal damage but whether these agents are capable of affecting gastric mucosal damage induced by strong irritants and healing of chronic gastric ulcers remains to be studied. In this investigation, effects of nitric oxide-releasing aspirin and nitric oxide-releasing naproxen were compared with those of native agents on gastric lesions provoked by 100% ethanol and on healing of chronic acetic acid ulcers. Results. Both, nitric oxide-releasing aspirin and naproxen dose-dependently attenuated ethanol-induced damage and produced a significant rise in gastric blood flow but did not delay healing of gastric ulcers while native aspirin and naproxen had no influence on ethanol-induced gastric damage but significantly prolonged ulcer healing, reduced gastric blood flow and suppressed mucosal generation of prostaglandin E2. The gastroprotective and hyperemic effects of both nitric oxide-non-steroidal anti-inflammatory drugs were completely abolished by ODQ, an inhibitor of guanylyl cyclase-cGMP system but not influenced by suppression of nitric oxide-synthase with L-NNA. The damaging effects of native acetyl salicylate acid or naproxen were aggravated by acidification of these non-steroidal anti-inflammatory drugs but the exogenous acid added to nitric oxide-acetyl salicylate acid or nitric oxide-naproxen failed to influence their effect. Despite inhibiting of PGE2 generation, both nitric oxide-releasing derivs. and native aspirin and naproxen failed to affect expression of cyclooxygenase-1 mRNA but upregulated the cyclooxygenase-2 mRNA. Concurrent inhibition of cyclooxygenase-2 by selective inhibitor NS-398 which by itself delayed ulcer healing and attenuated the gastric blood flow at ulcer margin, significantly worsened the effects of these nitric oxide-non-steroidal anti-inflammatory drugs and their parent drugs on ulcer healing and the gastric blood flow at the ulcer margin. Conclusions. Coupling of nitric oxide to aspirin or naproxen attenuates ethanol-induced damage, possibly due to an increase in gastric microcirculation mediated by excessive release and action of nitric oxide that probably compensates for PG deficiency induced by non-steroidal anti-inflammatory drugs; and nitric oxide-non-steroidal anti-inflammatory drug, unlike classic non-steroidal anti-inflammatory drugs, does not affect intact gastric mucosa and fails to delay the healing of

pre-existing ulcers.
ST nitric oxide aspirin gastroprotective ulcer healing; naproxen nitric oxide gastroprotective ulcer healing; nonsteroidal antiinflammatory drug nitric oxide gastroprotective
IT Circulation
(gastric; gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)
IT Wound healing
(gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)
IT Stomach, disease
(mucosa, injury; gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)
IT Anti-inflammatory agents
(nonsteroidal; gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)
IT Stomach, disease
(ulcer; gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)
IT 64-17-5, Ethanol, biological studies 64-19-7, Acetic acid, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)
IT **163133-43-5, HCT 3012** 175033-36-0, NCX 4016
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)
IT 50-78-2, Aspirin 22204-53-1, Naproxen
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)
IT 7665-99-8, CGMP 9054-75-5, Guanylyl cyclase 10102-43-9, Nitric oxide, biological studies 329900-75-6, cyclooxygenase-2 329967-85-3, cyclooxygenase-1
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)
IT 363-24-6, prostaglandin E2
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Anand, B; Am J Gastroenterol 1999, V94, P1818 HCAPLUS
(2) Brzozowski, T; Digestion 1993, V54, P24 MEDLINE
(3) Brzozowski, T; Eur J Pharmacol 1999, V374, P263 HCAPLUS
(4) Brzozowski, T; Eur J Pharmacol 1999, V385, P47 HCAPLUS
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(15) Kennedy, B; Biochem Biophys Res Commun 1993, V197, P494 MEDLINE
(16) Konturek, P; Aliment Pharmacol Ther 1998, V12, P767 HCAPLUS

(17) Konturek, P; Gastroenterology 1990, V99, P1607 HCAPLUS
(18) Konturek, S; Digestion 1991, V49, P140 HCAPLUS
(19) Konturek, S; Eur J Pharmacol 1993, V239, P215 HCAPLUS
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(21) Lefebre, R; Br J Pharmacol 1998, V124, P1439
(22) Levi, S; Lancet 1990, V336, P840 HCAPLUS
(23) Mizuno, H; Gastroenterology 1997, V12, P387
(24) Moncada, S; Pharmacol Rev 1991, V43, P109 HCAPLUS
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(26) O'Banion, M; Proc Natl Acad Sci 1992, V89, P4888 HCAPLUS
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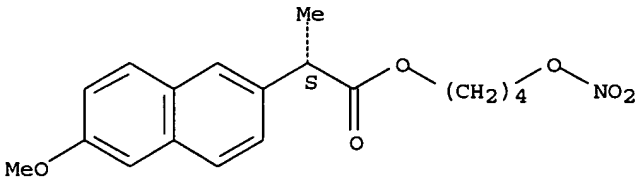
(31) Vane, J; Inflamm Res 1995, V44, P1 HCAPLUS
(32) Vane, J; Inflamm Res 1998, V47, P78
(33) Wallace, J; Am J Physiol 1997, V273, P1246
(34) Wallace, J; Eur J Pharmacol 1994, V257, P249 HCAPLUS
(35) Wallace, J; Eur J Pharmacol 1995, V280, P63 HCAPLUS
(36) Wallace, J; J Clin Invest 1995, V96, P2711 HCAPLUS
(37) Wang, J; Gastroenterology 1989, V96, P393 HCAPLUS
(38) Whittle, B; Br J Pharmacol 1990, V99, P607 HCAPLUS

IT **163133-43-5, HCT 3012**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gastroprotective and ulcer healing effects of nitric oxide-releasing non-steroidal anti-inflammatory drugs)

RN 163133-43-5 HCAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L17 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:861483 HCAPLUS
DN 134:25340
ED Entered STN: 08 Dec 2000
TI New use of compounds as antibacterial agents
IN Eek, Arne; Raud, Johan
PA Astrazeneca AB, Swed.
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-04
ICS A61K031-196; A61K031-33; A61P001-04; A61P031-00
CC 1-5 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000072838	A1	20001207	WO 2000-SE1071	20000525 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,

SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA	2373653	AA	20001207	CA 2000-2373653	20000525 <--
BR	2000011116	A	20020219	BR 2000-11116	20000525 <--
EP	1196155	A1	20020417	EP 2000-937451	20000525 <--
EP	1196155	B1	20040804		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO

TR	200103474	T2	20020422	TR 2001-200103474	20000525 <--
JP	2003500442	T2	20030107	JP 2000-620950	20000525 <--
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NZ	515317	A	20040528	NZ 2000-515317	20000525 <--
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AU	780678	B2	20050407	AU 2000-52623	20000525 <--
RU	2252032	C2	20050520	RU 2001-135826	20000525 <--
US	6593339	B1	20030715	US 2000-673007	20000929 <--
ZA	2001009497	A	20030217	ZA 2001-9497	20011116 <--
BG	106158	A	20020628	BG 2001-106158	20011128 <--
NO	2001005855	A	20020130	NO 2001-5855	20011130 <--
HK	1045814	A1	20050401	HK 2002-107373	20021009 <--
US	2004048917	A1	20040311	US 2003-426952	20030501 <--

PRAI	SE 1999-2027	A	19990601	<--
	SE 1999-4704	A	19991221	<--
	WO 2000-SE1071	W	20000525	<--
	US 2000-673007	A1	20000929	<--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000072838	ICM	A61K031-04
	ICS	A61K031-196; A61K031-33; A61P001-04; A61P031-00
WO 2000072838	ECLA	A61K031/00+A; A61K031/407; A61K045/06; A61K031/21; A61K031/215L5; A61K031/216; A61K031/381; A61K031/403; A61K031/4035; A61K031/405 <--
US 6593339	NCL	514/303.000; 514/165.000; 514/166.000; 514/333.000; 514/338.000; 514/926.000; 514/927.000
	ECLA	A61K031/00+A; A61K031/4035; A61K031/405; A61K031/407; A61K045/06; A61K031/21; A61K031/215L5; A61K031/216; A61K031/381; A61K031/403 <--
US 2004048917	NCL	514/417.000; 514/448.000; 514/509.000
	ECLA	A61K031/00+A; A61K031/21; A61K031/215L5; A61K031/216; A61K031/381; A61K031/403; A61K031/4035; A61K031/405; A61K031/407; A61K045/06 <--

AB The present invention discloses a new use of NO-releasing NSAIDs, especially NO-releasing NSAIDs of formula (I), or a pharmaceutically acceptable salt or enantiomer thereof, for the manufacture of a medicament for the treatment of bacterial infections, especially caused or mediated by Helicobacter pylori. Disclosed is also the new use of a NO-releasing NSAID in combination with an acid susceptible proton pump inhibitor for the treatment of bacterial infections.

ST antibacterial Helicobacter NSAID nitric oxide; proton pump inhibitor Helicobacter NSAID nitric oxide

IT Anti-inflammatory agents
(nonsteroidal; treatment of Helicobacter pylori infections with nitric oxide-releasing NSAIDs and proton pump inhibitors)

IT Antibacterial agents
Helicobacter pylori
(treatment of Helicobacter pylori infections with nitric oxide-releasing NSAIDs and proton pump inhibitors)

IT 9000-83-3, ATPase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hydrogen ion-translocating, inhibitors; treatment of Helicobacter pylori infections with nitric oxide-releasing NSAIDs and proton pump inhibitors)

IT 73590-58-6, Omeprazole 103577-45-3, Lansoprazole 119141-88-7, (S)-Omeprazole 156661-01-7 156970-83-1 164790-48-1 170591-17-0 174454-43-4 174454-51-4 311336-57-9 311336-58-0 311336-59-1 311336-60-4 311336-61-5 311336-62-6 311336-63-7 311336-64-8 311336-65-9 311336-66-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of Helicobacter pylori infections with nitric oxide-releasing NSAIDs and proton pump inhibitors)

IT 10102-43-9, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of Helicobacter pylori infections with nitric oxide-releasing NSAIDs and proton pump inhibitors)

RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD

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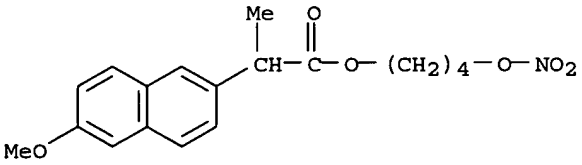
IT 170591-17-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of Helicobacter pylori infections with nitric oxide-releasing NSAIDs and proton pump inhibitors)

RN 170591-17-0 HCAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester (9CI) (CA INDEX NAME)



L17 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:618129 HCAPLUS

DN 133:290916

ED Entered STN: 06 Sep 2000

TI Antihypertensive properties of a nitric oxide-releasing naproxen derivative in two-kidney, one-clip rats

AU Muscara, Marcelo N.; McKnight, Webb; Lovren, Fina; Triggle, Christopher R.; Cirino, Giuseppe; Wallace, John L.

CS Department of Pharmacology and Therapeutics, University of Calgary, Calgary, AB, T2N 4N1, Can.

SO American Journal of Physiology (2000), 279(2, Pt. 2), H528-H535
CODEN: AJPHAP; ISSN: 0002-9513

PB American Physiological Society

DT Journal

LA English

CC 1-8 (Pharmacology)

AB Nonsteroidal anti-inflammatory drugs have been reported to exacerbate

hypertension. In this study, we tested the hypothesis that a nitric oxide-releasing derivative of naproxen would ameliorate hypertension in the rat. Hypertension was induced by partially occluding one renal artery (the "2K,1C" model), and 2 wk later the rats started receiving naproxen, the nitric oxide-releasing derivative **HCT-3012**, or vehicle each day for 2 wk. Naproxen significantly exacerbated the hypertension. **HCT-3012** significantly reduced blood pressure relative to both the naproxen- and vehicle-treated groups. Both naproxen and **HCT-3012** markedly suppressed whole blood thromboxane B2 synthesis. In studies of anesthetized rats, naproxen significantly enhanced the late hypertensive response to endothelin-1 and significantly blunted the early hypotensive response. In contrast, HCT-3102 did not affect either response to endothelin-1. In vitro, **HCT-3012** significantly reduced the responsiveness of aortic rings to the contractile effects of phenylephrine. These studies suggest that **HCT-3012** reduces blood pressure in hypertensive rats, not simply through the vasodilatory actions of the nitric oxide it releases, but through alterations in the responsiveness of the vasculature to endogenous pressor agents.

ST antihypertensive nitric oxide naproxen deriv **HCT3012**

IT Antihypertensives
Vasodilators
(antihypertensive properties of a nitric oxide-releasing naproxen derivative in two-kidney, one-clip rats)

IT Anti-inflammatory agents
(nonsteroidal; antihypertensive properties of a nitric oxide-releasing naproxen derivative in two-kidney, one-clip rats)

IT 22204-53-1, Naproxen
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(antihypertensive properties of a nitric oxide-releasing naproxen derivative in two-kidney, one-clip rats)

IT 22204-53-1D, derivs. 123626-67-5, Endothelin-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antihypertensive properties of a nitric oxide-releasing naproxen derivative in two-kidney, one-clip rats)

IT 10102-43-9, Nitric oxide, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(donors; antihypertensive properties of a nitric oxide-releasing naproxen derivative in two-kidney, one-clip rats)

IT 54397-85-2, Thromboxane B2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis; antihypertensive properties of a nitric oxide-releasing naproxen derivative in two-kidney, one-clip rats)

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L17 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:557438 HCAPLUS
DN 133:232547
ED Entered STN: 14 Aug 2000
TI NO-naproxen modulates inflammation, nociception and downregulates T cell response in rat Freund's adjuvant arthritis
AU Cicala, Carla; Ianaro, Angela; Fiorucci, Stefano; Calignano, Antonio; Bucci, Mariarosaria; Gerli, Roberto; Santucci, Luca; Wallace, John L.; Cirino, Giuseppe
CS Dipartimento di Farmacologia Sperimentale, Universita degli Studi di Napoli - Federico II, Naples, 80131, Italy
SO British Journal of Pharmacology (2000), 130(6), 1399-1405
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Anti-inflammatory non steroidal drugs releasing NO (NO-NSAIDs) are a new class of anti-inflammatory drugs to which has been added an NO-releasing moiety. These compds. have been shown to retain the anti-inflammatory, analgesic and antipyretic activity of the parent compound but to be devoid of gastrointestinal (GI) toxicity. Freund's adjuvant (FA) arthritis was induced in rats by a single intraplantar injection into the right hindpaw of 100 μl of mycobacterium butyricum (6 mg ml-1). The effect of equimolar doses of naproxen (1, 3 and 10 mg kg-1) and NO-naproxen (1.5, 4.5 and 16 mg kg-1) was evaluated using two dosage regimen protocols: (i) preventive, starting oral administration of the drugs at the time of induction of arthritis and for the following 21 days (day 1-21); (ii) therapeutic, starting oral administration of the drugs 7 days after adjuvant injection and for the following 14 days (day 7-21). Hindpaw swelling (days 3, 7, 11, 14, 17, 21) and nociception (days 15 and 21) were measured. On day 22 rats were sacrificed, draining lymph nodes were removed and T cells isolated. In vitro proliferation of T cells following stimulation with Con A (0.5-5 μg ml-1) was measured using a tritiated thymidine incorporation assay. IL-2 receptor expression on T cells was measured by FACS anal. Naproxen and NO-naproxen showed similar activity in reducing edema formation in the non-injected (controlateral) hindpaw. Both drugs showed anti-nociceptive effect. NO-naproxen was anti-nociceptive at a dose of 4.5 mg kg-1 while naproxen showed the same extent of inhibition only at a dose of 10 mg kg-1. T cells were isolated and characterized by FACS anal. Stimulation of isolated T cells with concanavallin A in vitro caused a significant increase in thymidine uptake. NO-naproxen at a dose of 4.5 mg kg-1 inhibited T cell proliferation to the same extent as 10 mg kg-1 of naproxen. Inhibition of T cell proliferation was well correlated with reduced IL-2 receptor expression on T cells. In addition, NO-naproxen reduced both IL-1β and TNFα plasma levels while naproxen reduced IL-1β levels only.
In conclusion, both naproxen and NO-naproxen reduce inflammation and nociception associated with arthritis. In addition NO-naproxen interferes to a larger extent with cellular mechanism involved in T cell activation in rat adjuvant arthritis indicating that introduction of the NO moiety in the

naproxen structure increases the effect at the level of the immune system.
ST **nitronaproxen** antiinflammatory analgesic T cell; antiarthritic **nitronaproxen** naproxen nitric oxide
IT Analgesics
Antiarthritics
T cell (lymphocyte)
(NO-naproxen modulates inflammation, nociception and downregulates T cell response in arthritis)
IT Interleukin 1β
Interleukin 2 receptors
Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NO-naproxen modulates inflammation, nociception and downregulates T cell response in arthritis)
IT Cell proliferation
(T cell; NO-naproxen modulates inflammation, nociception and downregulates T cell response in arthritis)
IT Anti-inflammatory agents
(nonsteroidal; NO-naproxen modulates inflammation, nociception and downregulates T cell response in arthritis)
IT **163133-43-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NO-naproxen modulates inflammation, nociception and downregulates T cell response in arthritis)
IT 10102-43-9, Nitric oxide, biological studies 22204-53-1, Naproxen
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NO-naproxen modulates inflammation, nociception and downregulates T cell response in arthritis)
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
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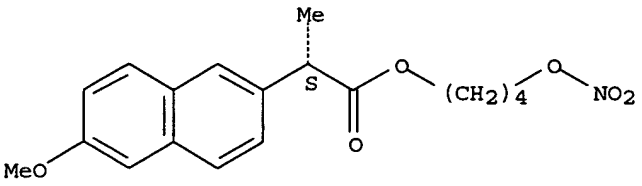
IT **163133-43-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NO-naproxen modulates inflammation, nociception and downregulates T

cell response in arthritis)
RN 163133-43-5 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L17 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:171920 HCAPLUS
DN 132:317766
ED Entered STN: 16 Mar 2000
TI Wound collagen deposition in rats: effects of an NO-NSAID and a selective COX-2 inhibitor
AU Muscara, Marcelo N.; McKnight, Webb; Asfaha, Samuel; Wallace, John L.
CS Department of Pharmacology & Therapeutics, University of Calgary, Calgary, AB, T2N 4N1, Can.
SO British Journal of Pharmacology (2000), 129(4), 681-686
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
CC 1-7 (Pharmacology)
AB 1 Selective cyclo-oxygenase (COX)-2 inhibitors and nitric oxide-releasing nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit reduced toxicity in the gastrointestinal tract, but may affect wound healing in other tissues. In this study, we have compared the effects of a selective COX-2 inhibitor (celecoxib), a nitric-oxide releasing derivative of naproxen (**HCT-3012**) and naproxen in a model of wound collagen deposition in the rat. 2 Polyvinyl alc. sponges were implanted s.c. in rats. The rats were treated daily for 5 days with the test drugs at equieffective anti-inflammatory doses. 3 Naproxen (10 mg.kg-1) significantly decreased (45%) collagen deposition at the wound site relative to the vehicle-treated control group. In contrast, **HCT-3012** (14.5 mg kg-1) significantly increased (62%) collagen deposition, while celecoxib (10 mg kg-1) had no effect. 4 Naproxen and **HCT-3012** suppressed prostaglandin (PG) E2 levels at the wound site and whole blood thromboxane synthesis to similar degrees. Celecoxib had no significant effect on wound fluid PGE2 levels, but slightly reduced whole blood thromboxane synthesis (by 17%). 5 COX-1 mRNA and protein were expressed in the wound exudate, the skin surrounding the wound and in normal skin. In contrast, COX-2 mRNA, but not protein, was expressed in wound and normal skin. 6 These results demonstrate that **HCT-3012** can significantly enhance collagen deposition at a wound site, despite inhibiting prostaglandin synthesis to the same extent as the parent drug. Nitric oxide-releasing NSAIDs may represent a safer alternative to standard NSAIDs for use as anti-inflammatory and analgesic agents by post-surgery patients.
ST NSAID naproxen nitric oxide wound healing; collagen deposition NSAID naproxen nitric oxide
IT Wound healing
(effects of nitric oxide-NSAID vs. a selective COX-2 inhibitor on wound collagen deposition in rats)
IT Collagens, biological studies
Thromboxanes
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(effects of nitric oxide-NSAID vs. a selective COX-2 inhibitor on wound collagen deposition in rats)
IT Anti-inflammatory agents
(nonsteroidal; effects of nitric oxide-NSAID vs. a selective COX-2 inhibitor on wound collagen deposition in rats)
IT 22204-53-1, Naproxen 22204-53-1D, derivs. 169590-42-5, Celecoxib
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of nitric oxide-NSAID vs. a selective COX-2 inhibitor on wound collagen deposition in rats)
IT 10102-43-9, Nitrogen oxide (NO), biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of nitric oxide-NSAID vs. a selective COX-2 inhibitor on wound collagen deposition in rats)
IT 363-24-6, Prostaglandin E2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(effects of nitric oxide-NSAID vs. a selective COX-2 inhibitor on wound collagen deposition in rats)
IT 39391-18-9, Cyclooxygenase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitors; effects of nitric oxide-NSAID vs. a selective COX-2 inhibitor on wound collagen deposition in rats)
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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L17 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:257300 HCAPLUS

DN 131:97177
ED Entered STN: 27 Apr 1999
TI Nitric oxide-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα
AU Fiorucci, S.; Santucci, L.; Federici, B.; Antonelli, E.; Distrutti, E.; Morelli, O.; Renzo, G. Di; Coata, G.; Cirino, G.; Soldato, P. Del; Morelli, A.
CS Clinica di Gastroenterologia ed Epatologia, Policlinico Monteluce, Perugia, 06100, Italy
SO Alimentary Pharmacology and Therapeutics (1999), 13(3), 421-435
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Science Ltd.
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Background: Nitric oxide (NO)-releasing NSAIDs are a new class of NSAID derivs. with markedly reduced gastrointestinal toxicity. Although it has been demonstrated that NO-NSAIDs spare gastric mucosal blood flow, mol. determinants involved in this effect are unknown. Aim: To investigate the effect of aspirin, naproxen and flurbiprofen, and their NO-derivs., on gastric apoptosis and endothelial cell damage induced by tumor necrosis factor-α (TNFα). In other systems, TNFα-induced apoptosis is mediated by caspases, a growing family of cysteine proteases similar to the IL-1β converting enzyme (ICE), and so we have investigated whether NO-NSAIDs modulate ICE-like endopeptidases. Methods: Rats were treated orally with aspirin, naproxen and flurbiprofen, or their NO-releasing derivs. in equimolar doses, and were killed 3 h later to assess mucosal damage and caspase activity. Endothelial cells (HUVECs) were obtained from human umbilical cord by enzymic digestion. Caspase 1 and 3 activities were measured by a fluorimetric assay using selective peptides as substrates and inhibitors. Apoptosis was quantified by ELISA specific for histone-associated DNA fragments and by the terminal transferase nick-end translation method (TUNEL). Results: In vivo NSAID administration caused a time-dependent increase in gastric mucosal damage and caspase activity. NCX-4016, NO-naproxen and NO-flurbiprofen did not cause any mucosal damage and prevented cysteine protease activation. NSAIDs and NO-NSAIDs stimulated TNFα release. Exposure to TNFα resulted in a time- and concentration-dependent HUVEC apoptosis, an effect that was prevented by pretreating the cells with NCX-4016, NO-naproxen, NO-flurbiprofen, SNP or Z-VAD.FMK, a pan-caspase inhibitor. The activation of ICE-like cysteine proteases was required to mediate TNFα-induced apoptosis of HUVECs. Exogenous NO donors inhibited TNFα-induced cysteine protease activation. Inhibition of caspase activity was due to S-nitrosylation of ICE/CPP32-like proteases. NO-NSAIDs prevented IL-1β release from endotoxin-stimulated macrophages. Conclusions: NO-releasing NSAIDs are a new class of non-peptide caspase inhibitors. Inhibition of ICE-like cysteine proteases prevents endothelial cell damage induced by pro-inflammatory agents and might contribute to the gastro-protective effects of NO-NSAIDs.
ST nitric oxide NSAID gastrointestinal toxicity; cysteine protease nitric oxide NSAID; endothelial apoptosis TNFalpha nitric oxide NSAID
IT Apoptosis
(NO-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα)
IT Interleukin 1β
Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NO-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα)
IT Blood vessel
(endothelium; NO-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells

from apoptosis induced by TNFα)
IT Stomach, disease
(mucosa, injury; NO-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα)
IT Anti-inflammatory agents
(nonsteroidal; NO-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα)
IT Digestive tract
(toxicity; NO-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα)
IT 50-78-2, Aspirin 5104-49-4, Flurbiprofen 22204-53-1, Naproxen 158836-71-6, Nitroflurbiprofen 163133-43-5 175033-36-0, NCX 4016
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NO-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα)
IT 9001-92-7, Endopeptidase 169592-56-7, Caspase 3
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NO-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα)
IT 10102-43-9, Nitric oxide, biological studies 37353-41-6, Cysteine protease 122191-40-6, Interleukin-1β converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NO-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα)
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
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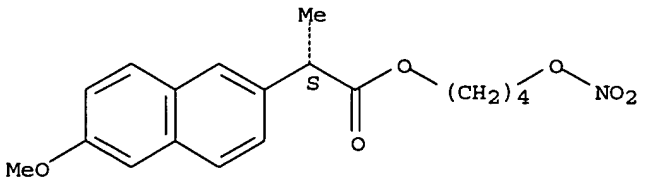
IT **163133-43-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NO-releasing NSAIDs inhibit interleukin-1β converting enzyme-like cysteine proteases and protect endothelial cells from apoptosis induced by TNFα)

RN 163133-43-5 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L17 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:181750 HCAPLUS
DN 128:303783
ED Entered STN: 28 Mar 1998
TI Effect of a nitric oxide-releasing naproxen derivative on hypertension and gastric damage induced by chronic nitric oxide inhibition in the rat
AU Muscara, Marcelo N.; McKnight, Webb; Del Soldato, Piero; Wallance, John L.
CS Dep. Pharmacology and Therapeutics, Univ. Calgary, Calgary, AB, Can.
SO Life Sciences (1998), 62(15), PL235-PL240
CODEN: LIFSAK; ISSN: 0024-3205
PB Elsevier Science Inc.
DT Journal
LA English
CC 1-7 (Pharmacology)
AB NSAIDs can elevate blood pressure through mechanisms such as renal vasoconstriction and sodium retention. These effects are particularly evident in hypertensive individuals. Nitric oxide-releasing NSAID derivs. have been shown to have greatly reduced toxicity in the gastrointestinal tract and kidney. We therefore evaluated the effects of a 4 wk treatment with either naproxen or its nitric oxide-releasing derivative (NO-naproxen) on systemic arterial blood pressure and gastric damage in rats in which hypertension was induced by L-NAME. Rats received either L-NAME dissolved

in the drinking water (400 mg/L) or tap water (control). Vehicle, naproxen (10 mg/kg) or an equimolar dose of NO-naproxen (14.5 mg/kg) were administered orally each day. After 4 wk, blood pressure was measured, blood samples were taken for measurement of thromboxane synthesis, and gastric damage was evaluated by blind, macroscopic scoring. Both naproxen and NO-naproxen inhibited systemic cyclooxygenase activity by >90%. NO-naproxen-treated rats exhibited no significant gastric damage. The gastric damage produced by L-NAME alone was potentiated by naproxen but prevented by NO-naproxen. L-NAME treatment significantly increased blood pressure. In the absence of L-NAME, the naproxen group had significantly higher blood pressure than both the control and NO-naproxen groups. IN rats receiving L-NAME, the same conclusions apply, but the concomitant administration of NO-naproxen was able to significantly reduce the blood pressure compared to L-NAME alone. Based on these results, we conclude that NO-naproxen may represent a safer alternative to standard NSAIDs in the treatment of inflammatory conditions in hypertensive patients.

ST NSAID nitric oxide hypertension naproxen antiinflammatory

IT Blood pressure
Hypertension
(adverse effects of NSAID NO-naproxen as antiinflammatory agent for hypertensive patients)

IT Stomach, disease
Stomach, disease
(injury; adverse effects of NSAID NO-naproxen as antiinflammatory agent for hypertensive patients)

IT Anti-inflammatory agents
(nonsteroidal; adverse effects of NSAID NO-naproxen as antiinflammatory agent for hypertensive patients)

IT 22204-53-1, Naproxen **163133-43-5**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adverse effects of NSAID NO-naproxen as antiinflammatory agent for hypertensive patients)

IT 10102-43-9, Nitric oxide, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(adverse effects of NSAID NO-naproxen as antiinflammatory agent for hypertensive patients)

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD

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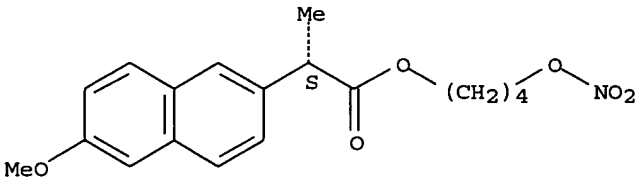
IT 163133-43-5
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adverse effects of NSAID NO-naproxen as antiinflammatory agent for hypertensive patients)
RN 163133-43-5 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

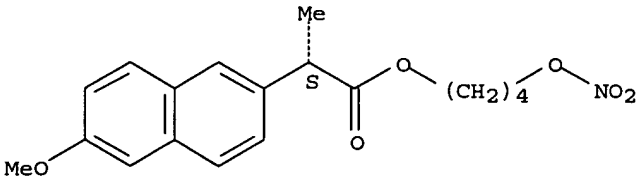
Absolute stereochemistry.



L17 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:180246 HCAPLUS
DN 126:220449
ED Entered STN: 17 Mar 1997
TI NO-naproxen vs. naproxen: ulcerogenic, analgesic and anti-inflammatory effects
AU Davies, N. M.; Roseth, A. G.; Appleyard, C. B.; Mcknight, W.; Del Soldato, P.; Calignano, A.; Cirino, G.; Wallace, J. L.
CS Intestinal Disease Research Unit, Faculty of Medicine, University of Calgary, Calgary, AB, Can.
SO Alimentary Pharmacology and Therapeutics (1997), 11(1), 69-79
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Studies were performed to determine if naproxen nitroxybutyl ester [NO-releasing naproxen (NO-naproxen)] was less ulcerogenic to the gastrointestinal tract than the parent naproxen, and if it exerted comparable analgesic and anti-inflammatory activities. The 2 drugs were compared in an acute gastric injury model, an antral ulcer model and after twice-daily administration for 18 days (small intestinal damage model) in rats. Anti-inflammatory activity was examined in the carrageenan-induced paw edema model in rats, while analgesia was examined in the HOAc-induced writhing model in mice. The pharmacokinetic profiles of naproxen vs. NO-naproxen were compared by HPLC. NO-naproxen produced less gastric damage than naproxen, despite inducing similar increases in plasma tumor necrosis factor-α. With chronic administration, small intestinal damage was markedly less with NO-naproxen than with the parent drug. However, NO-naproxen exerted analgesic effects superior to those of naproxen, and comparable anti-inflammatory effects. NO-naproxen was not completely converted to naproxen, but the lower plasma level of naproxen formed from NO-naproxen was not the underlying reason for the lower gastrointestinal toxicity of NO-naproxen. NO-naproxen represents a novel, gastrointestinal-sparing nonsteroidal anti-inflammatory drug with superior analgesic effects and comparable anti-inflammatory properties to those of naproxen.
ST naproxen deriv antiinflammatory analgesic ulcer induction; nonsteroidal antiinflammatory naproxen deriv
IT Intestine, disease

Intestine, disease
Stomach, disease
Stomach, disease
(injury; naproxen nitroxybutyl ester and naproxen induction of)
IT Analgesics
(naproxen nitroxybutyl ester and naproxen comparison as)
IT Ulcer
(naproxen nitroxybutyl ester and naproxen induction of)
IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(naproxen nitroxybutyl ester and naproxen induction of gastric damage in relation to production of)
IT Anti-inflammatory agents
(nonsteroidal; naproxen nitroxybutyl ester and naproxen comparison as)
IT **163133-43-5**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ulcerogenic, analgesic and anti-inflammatory effects of)
IT 22204-53-1, Naproxen
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ulcerogenic, analgesic and anti-inflammatory effects of naproxen nitroxybutyl ester in comparison with those of)
IT **163133-43-5**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ulcerogenic, analgesic and anti-inflammatory effects of)
RN 163133-43-5 HCAPLUS
CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L17 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:333513 HCAPLUS
DN 125:25397
ED Entered STN: 08 Jun 1996
TI Nitric oxide-releasing NSAIDs, a novel class of safe and effective anti-inflammatory agents
AU Del Soldato, P.; Cuzzolin, L.; Adami, A.; Conforti, A.; Crivellente, F.; Benoni, G.
CS Policlinico Borgo Roma, University of Verona, Verona, 37134, Italy
SO Inflammopharmacology (**1996**), 4(2), 181-188
CODEN: IAOAES; ISSN: 0925-4692
PB Kluwer
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 19 refs. The pharmacotoxicol. profile were reported for three new nitro-anti-inflammatory agents, nitrofenac, **nitronaproxen** and nitroflurbiprofen with the following results: in models of acute (carrageenan edema) and chronic (adjuvant arthritis)

inflammation in the rat, the nitro derivs., compared with the parent drugs, showed similar anti-inflammatory properties by significantly inhibiting both edema volume and arthritis development. The nitroso compds. showed markedly less ulcerogenic activity compared with the parent drugs both in acute conditions and at the end of the chronic inflammation test. The lack of gastrointestinal damage observed with these new anti-inflammatory drugs is the consequence of their ability to release NO. This hypothesis is supported by pharmacokinetic studies and a significant increase in nitrite/nitrate plasma levels.

ST review nonsteroidal antiinflammatory agent

IT Inflammation inhibitors
(nonsteroidal; nitric oxide-releasing nonsteroidal antiinflammatory agents)

IT 10102-43-9, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nitric oxide-releasing nonsteroidal antiinflammatory agents)

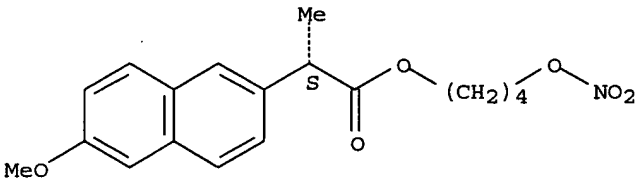
IT 156661-01-7, Nitrofenac 158836-71-6, Nitroflurbiprofen
163133-43-5, Nitronaproxen
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide-releasing nonsteroidal antiinflammatory agents)

IT **163133-43-5, Nitronaproxen**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide-releasing nonsteroidal antiinflammatory agents)

RN 163133-43-5 HCAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L17 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1996:253443 HCAPLUS

DN 124:332273

ED Entered STN: 30 Apr 1996

TI Inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivatives with gastrointestinal-sparing properties

AU Cirino, G.; Wheeler-Jones, C. P. D.; Wallace, J. L.; Del Soldato, P.; Baydoun, A. R.

CS Vascular Biology Research Centre, King's College, London, W8 7AH, UK

SO British Journal of Pharmacology (**1996**), 117(7), 1421-6
CODEN: BJPCBM; ISSN: 0007-1188

PB Stockton

DT Journal

LA English

CC 1-7 (Pharmacology)

AB The effects of novel nitric oxide-releasing nonsteroidal anti-inflammatory compds. (NO-NSAIDs) on induction of nitric oxide (NO) synthase by bacterial lipopolysaccharide (LPS) were examined in a murine cultured macrophage cell line, J774. LPS-induced nitrite production was markedly attenuated by the nitroxybutyl ester derivs. of flurbiprofen (FNBE), aspirin, ketoprofen, diclofenac and ketorolac, with each compound reducing accumulated nitrite levels by >40% at the maximum concns. (100 μg ml-1) used. Further examination revealed that nitrite production was inhibited in a concentration-dependent (1-100 μg ml-1) manner by FNBE which at 100 μg ml-1 decreased LPS stimulated levels by 63.3±8.6% (n=7). The parent compound flurbiprofen was relatively ineffective over the same concentration-range,

inhibiting nitrite accumulation by 24±0.9% (n=3) at the maximum concentration used (100 μg ml-1). FNBE reduced LPS-induced nitrite production when added to cells up to 4 h after LPS. Thereafter, FNBE caused very little or no reduction in nitrite levels. Furthermore NO-NSAIDs (100 μg ml-1) did not inhibit the metabolism of L-[3H]-arginine to citrulline by NO synthase isolated from LPS-activated macrophages. Western blot anal. demonstrated that NO synthase expression was markedly attenuated following co-incubation of J774 cell with LPS (1 μg ml-1; 24 h) and FNBE (100μg ml-1; 24 h). Thus taken together, these findings indicate that NO-NSAIDs inhibit induction of NO synthase without directly affecting enzyme activity. In conclusion our results indicate that NO-NSAIDs can inhibit the inducible L-arginine-NO pathway, and are capable of suppressing NO synthesis by inhibiting expression of NO synthase. The clin. implications of these findings remain to be established.

ST nitric oxide synthase inhibition nonsteroid antiinflammatory

IT Lipopolysaccharides
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(bacterial; inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivs. with gastrointestinal-sparing properties)

IT Digestive tract
(inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivs. with gastrointestinal-sparing properties)

IT Inflammation inhibitors
(nonsteroidal, inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivs. with gastrointestinal-sparing properties)

IT 74-79-3, L-Arginine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(-NO pathway; inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivs. with gastrointestinal-sparing properties)

IT 10102-43-9, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(-arginine pathway; inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivs. with gastrointestinal-sparing properties)

IT 156661-01-7 156970-83-1 158836-71-6 **163133-43-5**
164790-48-1 171781-26-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivs. with gastrointestinal-sparing properties)

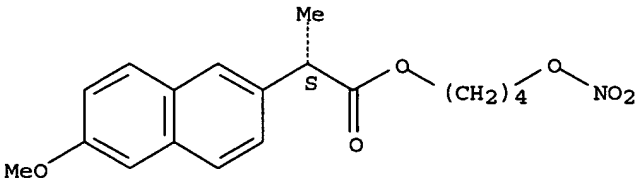
IT 125978-95-2, Nitric oxide synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivs. with gastrointestinal-sparing properties)

IT **163133-43-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of inducible nitric oxide synthase expression by novel nonsteroidal anti-inflammatory derivs. with gastrointestinal-sparing properties)

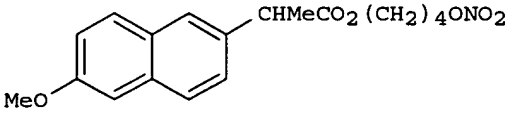
RN 163133-43-5 HCAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L17 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:498682 HCAPLUS
DN 122:281711
ED Entered STN: 20 Apr 1995
TI Anti-inflammatory potency and gastrointestinal toxicity of a new compound, **nitronaproxen**
AU Cuzzolin, L.; Conforti, A.; Adami, A.; Lussignoli, S.; Menestrina, F.; Del Soldato, P.; Benoni, G.
CS Institute of Pharmacology, University of Verona, Verona, 37134, Italy
SO Pharmacological Research (1995), 31(1), 61-5
CODEN: PHMREP; ISSN: 1043-6618
DT Journal
LA English
CC 1-7 (Pharmacology)
GI



I

AB Naproxen and its derivative **nitronaproxen** (I) at the doses of 5 and 10 mg kg-1 were compared for their acute anti-inflammatory efficacy in a carrageenan edema model and gastrointestinal toxicity in rats. Moreover, the effects of the two drugs were evaluated in the adjuvant arthritis, after chronic doses of 4 and 8 mg kg-1 administered orally for 18 days. The edema reduction was maintained much longer (until 5 h) with **nitronaproxen**; the inhibition of arthritis was 50% or more with both doses of the examined drugs. From the histol. examination of the stomachs, an extensive mucosal vasocongestion and hemorrhagic lesions have been observed in some rats treated with naproxen. The percentages of animals with ulcers were 50, 100 and 10 with naproxen 6 and 18 mg kg-1 and **nitronaproxen** 54 mg kg-1, resp. A better gastrointestinal tolerability has been observed in arthritic and edemic rats treated with **nitronaproxen** compared to naproxen: this could be due to the presence of nitric oxide that acts in maintaining the tissue perfusion and integrity.

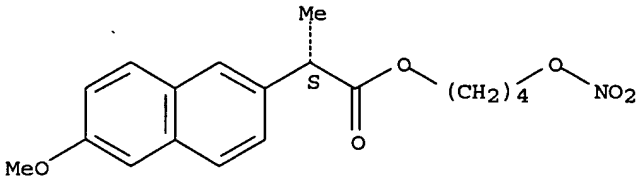
ST naproxen **nitronaproxen** antiinflammatory gastrointestinal toxicity
IT Digestive tract
Inflammation inhibitors
(anti-inflammatory activity and gastrointestinal toxicity of naproxen and **nitronaproxen**)
IT 22204-53-1, Naproxen **163133-43-5, Nitronaproxen**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-inflammatory activity and gastrointestinal toxicity of naproxen and **nitronaproxen**)
IT **163133-43-5, Nitronaproxen**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-inflammatory activity and gastrointestinal toxicity of naproxen and **nitronaproxen**)

RN 163133-43-5 HCAPLUS

CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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FILE LAST UPDATED: 15 Jun 2005  (20050615/ED)

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L1   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2001:115100  HCAPLUS
DN   134:178355
ED   Entered STN:  15 Feb 2001
TI   Process for the preparation of naproxene nitroxyalkyl esters
IN   Benedini, Francesca; Oldani, Erminio; Castaldi, Graziano; Tarquini,
     Antonio
PA   Nicox S.A., Fr.
SO   PCT Int. Appl., 16 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C07C203-04
CC   25-24 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
FAN.CNT 1
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
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CLASS

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US 6700011	NCL	558/482.000	
	ECLA	C07C203/04	<--
US 2005119339	NCL	514/510.000; 558/482.000	<--

OS CASREACT 134:178355; MARPAT 134:178355

AB A process for obtaining nitroxyalkyl esters of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid having an enantiomeric excess higher than or equal to 95 %, preferably higher than or equal to 98 %, was characterized in that a halide of the 2-(S)-(6-methoxy-2-naphthyl)propanoic acid of formula A-Hal, wherein A is the acid acyl residue, is reacted in an inert organic solvent with an aliphatic nitroxyalkanol HO-Y-ONO2, wherein Y is a C2-C20 alkylene or a cycloalkylene from 3 to 8 carbon atoms, or an alkylene as defined containing a cycloalkylene as defined, in the presence of an inorg. base. E.g., to a solution of 4-nitroxybutan-1-ol and K2CO3 in dichloromethane is added 2-(S)-(6-methoxy-2-naphthyl)propanoic acid chloride. to give the 4-nitroxybutyl ester of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (85%, ee 98%).

ST naproxene nitroxyalkyl ester prepn; naproxen nitroxyalkyl ester prepn

IT 163133-43-5P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of naproxene nitroxyalkyl esters)

IT 22204-53-1, Naproxen 22911-39-3 51091-84-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of naproxene nitroxyalkyl esters)

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RE.CNT  5     THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Hoechst Marion Roussel Inc; FR 2757159 A 1998 HCAPLUS
(2) Italfarmaco Spa; WO 9201668 A 1992 HCAPLUS
(3) Nicox Ltd; WO 9509831 A 1995 HCAPLUS
(4) Nicox Ltd; WO 9530641 A 1995 HCAPLUS
(5) Nicox Sa; WO 9716405 A 1997 HCAPLUS


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DICTIONARY FILE UPDATES:  15 JUN 2005  HIGHEST RN 852355-71-6

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*                                                                   *
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* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                   *
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http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide l3 tot

L3   ANSWER 1 OF 4  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   163133-43-5  REGISTRY
ED   Entered STN:  19 May 1995
CN   2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl
     ester, (αS)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, 4-(nitrooxy)butyl
     ester, (S)-
OTHER NAMES:
CN   (S)-2-(6-Methoxy-2-naphthyl)propanoic acid 4-nitrooxybutyl ester
CN   AZD 3582
CN   HCT 3012
CN   Nitronaproxen
FS   STEREOSEARCH
MF   C18 H21 N O6
SR   CA
LC   STN Files:   ADISINSIGHT, ADISNEWS, BIOSIS, CA, CAPLUS, CASREACT, CIN,
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Absolute stereochemistry.
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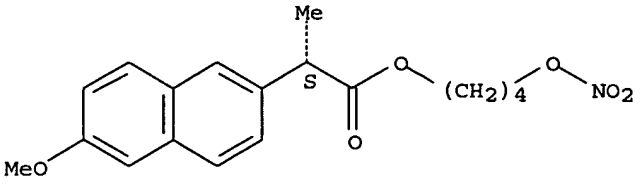

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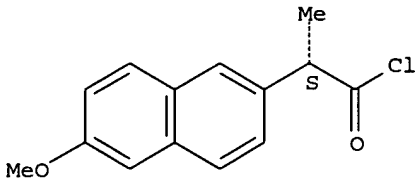
26 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN **51091-84-0** REGISTRY
ED Entered STN: 16 Nov 1984
CN 2-Naphthaleneacetyl chloride, 6-methoxy-α-methyl-, (αS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Naphthaleneacetyl chloride, 6-methoxy-α-methyl-, (S)-
OTHER NAMES:
CN (+)-Naproxen acid chloride
CN (2S)-2-(6-Methoxy(2-naphthyl)propanoyl chloride
CN (S)-2-(6-Methoxynaphth-2-yl)propionyl chloride
CN (S)-Naproxen chloride
CN d-2-(6-Methoxy-2-naphthyl)propionyl chloride
CN Naproxen acid chloride
CN Naproxen chloride
CN S-(+)-Naproxen chloride
FS STEREOSEARCH
MF C14 H13 Cl O2
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, IFICDB, IFIPAT, IFIUDB, IPA, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



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75 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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RN **22911-39-3** REGISTRY
ED Entered STN: 16 Nov 1984
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OTHER NAMES:
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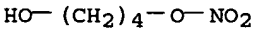

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RN 22204-53-1 REGISTRY
ED Entered STN: 16 Nov 1984
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(CA INDEX NAME)
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CN 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (S)-
OTHER NAMES:
CN (+)-(S)-Naproxen
CN (+)-2-(6-Methoxy-2-naphthyl)propionic acid
CN (+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid
CN (+)-Naproxen
CN (S)-(+)-2-(6-Methoxy-2-naphthyl)propionic acid
CN (S)-(+)-Naproxen
CN (S)-(+)-Naproxene
CN (S)-2-(6-Methoxy-2-naphthyl)propanoic acid
CN (S)-2-(6-Methoxy-2-naphthyl)propionic acid
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CN (S)-Naproxen
CN Apo-Naproxen
CN Bonyl
CN CG 3117
CN d-2-(6-Methoxy-2-naphthyl)propionic acid
CN d-Naproxen
CN Diocodal
CN Dysmenalgit
CN Equiproxen
CN Floginax
CN Laraflex
CN Laser
CN MNPA
CN Naixan
CN Napren
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CN Xenar
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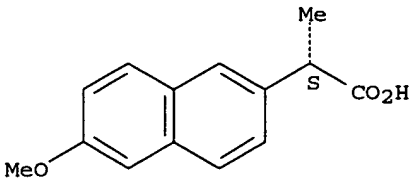
CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSPATENTS, IPA, MEDLINE, MRCK*, MSDS-OHS, PHAR, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (+).



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178 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4393 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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MOST RECENT DERWENT UPDATE: 200537 <200537/DW>
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L4 ANSWER 1 OF 1 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-218262 [22] WPIX
DOC. NO. CPI: C2001-065118
TITLE: Preparation of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid nitroxyalkylesters (naproxene) comprises reacting a 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid halide with a nitroxyalkanol in the presence of an inorganic base.

DERWENT CLASS: B05
INVENTOR(S): BENEDINI, F; CASTALDI, G; OLDANI, E; TARQUINI, A
PATENT ASSIGNEE(S): (NICO-N) NICOX SA
COUNTRY COUNT: 84
PATENT INFORMATION:

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RU 2248348	C2	20050320	(200521)			C07C203-04
US 2005119339	A1	20050602	(200537)			A61K031-21<--

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Search done by Noble Jarrell

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		RU 2002-102860	20000727	
US 2005119339	A1 Div ex	WO 2000-EP7222	20000727	<--
	Div ex	US 2002-31412	20020118	
		US 2003-625558	20030724	

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000064385	A	Based on	WO 2001010814
EP 1200386	A1	Based on	WO 2001010814
BR 2000012915	A	Based on	WO 2001010814
HU 2002002435	A2	Based on	WO 2001010814
JP 2003506425	W	Based on	WO 2001010814
EP 1200386	B1	Based on	WO 2001010814
DE 60005682	E	Based on	EP 1200386
		Based on	WO 2001010814
NZ 516699	A	Based on	WO 2001010814
EP 1384707	A1	Div ex	EP 1200386
US 6700011	B1	Based on	WO 2001010814
ES 2208390	T3	Based on	EP 1200386
AU 778694	B2	Previous Publ.	AU 2000064385
		Based on	WO 2001010814
RU 2248348	C2	Based on	WO 2001010814
US 2005119339	A1	Div ex	US 6700011

PRIORITY APPLN. INFO: **IT 1999-MI1753**
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ADDITIONAL: C07B053-00; C07B061-00
INDEX: C07M007:00

BASIC ABSTRACT:

WO 200110814 A UPAB: 20010421

NOVELTY - Preparation of nitroxyalkylesters of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid with an enantiomeric excess greater than 97% comprises reacting a 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid halide with an aliphatic nitroxyalkanol of formula (I) in an inert solvent in the presence of an inorganic base.

DETAILED DESCRIPTION - A process for preparation of nitroxyalkylesters of 2-(S)-6-methoxy-2-naphthyl)propanoic acid (I) (naproxene) having an enantiomeric excess higher than or equal to 97% comprises reaction of a 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid halide with an aliphatic nitroxyalkanol of formula (II) in an inert solvent in the presence of an inorganic base.

A-O-Y-ONO2 HO-Y-ONO2
(I) (II)

Y = 1-20C alkylene, 3-8C cycloalkylene (optionally substituted by 1-2 of 1-20C alkylene and/or 1 or more 1-20C alkyl), 5-6C aromatic (optionally substituted by 1-2 of 1-20C alkylene and/or 1 or more 1-20C alkyl or COOH), -(T)p-(CH(CH2ONO2)-CH2O)nf'-(T)- or -(T)p-(CH2-CH(ONO2)-CH2O)nf'-(T)-;

T = 1-20C alkylene;

p = 0 - 1;

nf' = 1 - 6; and

A = acyl residue of the acid.

USE - The process is useful for giving naproxene nitroxyalkylesters

in high enantiomeric excess.
ADVANTAGE - The reactions provide nitroxyalkylesters of 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid in higher enantiomeric excess and in higher yield than previous methods through the use of inorganic bases.
Dwg.0/0
FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B10-C04B; B10-G02; B10-G03

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